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Mycophenolate Mofetil Reduces Intimal Thickness by Intravascular Ultrasound After Heart Transplant: Reanalysis of the Multicenter Trial

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The mycophenolate mofetil (MMF) trial involved 650 heart transplant patients from 28 centers who received MMF or azathioprine (AZA), both in combination with cyclosporine and corticosteroids. Baseline and 1-year intravascular ultrasound (IVUS) were performed in 196 patients (102 MMF and 94 AZA) with no differences between groups in IVUS results analyzed by morphometric analysis (average of 10 evenly spaced sites, without matching sites between studies). Baseline to first-year IVUS data can also be analyzed by site-to-site analysis (matching sites between studies), which has been reported to be more clinically relevant. Therefore, we used site-to-site analysis to reanalyze the multicenter MMF IVUS data. Results: IVUS images were reviewed and interpretable in 190 patients (99 MMF and 91 AZA) from the multicenter randomized trial. The AZA group compared to the MMF group had a larger number of patients with first-year maximal intimal thickness (MIT) $\geq$0.3 mm (43% vs. 23%, $p = 0.005$), a greater decrease in the mean lumen area ($p = 0.02$) and a decrease in the mean vessel area (the area actually increased in the MMF group, $p = 0.03$). Conclusion: MMF-treated heart transplant patients compared to AZA-treated patients, both concurrently on cyclosporine and corticosteroids, in this study have significantly less progression of first-year intimal thickening.

Key words: Cardiac allograft vasculopathy, heart transplant, intravascular ultrasound, mycophenolate mofetil

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Introduction

The mycophenolate mofetil (MMF) multicenter trial was the first large-scale, randomized, double-blind, active-controlled clinical trial involving heart transplant patients (1). This study involved 650 heart transplant patients from 28 centers who received MMF or azathioprine (AZA), in addition to cyclosporine and corticosteroids. Of the 650 patients enrolled in this trial, 72 patients did not receive any study drug because they were unable to take oral study medication within 5 days of transplantation. This treated population (those patients who received at least one dose of the study drug) did not differ from the enrolled population with respect to baseline characteristics and demographics. This study showed that in patients receiving the study drug, the use of MMF resulted in a significant reduction in treated-rejection episodes and in mortality at 1 year post transplantation. Baseline and 1-year intravascular ultrasound (IVUS) studies were performed using morphometric analysis in 196 patients (102 MMF and 94 AZA patients) with no significant differences found in the results between the two study groups.

First-year IVUS measurements, including the change from baseline to 1-year maximal intimal thickness (MIT), have been reported to be a surrogate marker for long-term outcome after heart transplantation (2–4). This IVUS measurement most likely represents a heightened immune response of the recipient to the donor heart, which can lead to cardiac allograft vasculopathy (CAV) and subsequent poor outcome (5). First-year IVUS data (baseline to 1 year) can be analyzed using site-to-site analysis (used in recent reports) or by morphometric analysis (average of 10 sites, without matching sites) as performed in the MMF trial (6). Since intimal thickness is heterogeneous with most sites having little or no intimal thickening, morphometric analysis will not be sensitive to detect changes at any one particular site, as it averages data from multiple (usually 10) sites. Morphometric analysis of the first-year MMF IVUS data may not have accurately depicted the impact of MMF on first-year MIT in the study patients. Therefore,

the IVUS data from the randomized multicenter MMF trial was restudied using matched site-to-site analysis.

Methods

The original MMF trial was a multicenter, double-blind, active-controlled trial that involved 650 heart transplant patients from 28 centers who received MMF (3000 mg/kg/day) or AZA (1.5–3.0 mg/kg/day), in addition to cyclosporine and corticosteroids. Details of the protocol have been published previously (1).

IVUS was performed at baseline (4–6 weeks after transplant) and at 1 year. There were 190 study patients (treated population) with baseline and 1-year IVUS studies (MMF, N = 99 patients and AZA, N = 91 patients). IVUS data from 6 patients (3 patients from each group) were excluded due to the poor quality of the tapes preventing acceptable analysis. IVUS tapes (baseline and 1-year follow-up) from each patient were evaluated at a Core Laboratory (University of California at Los Angeles) for analysis. The IVUS tapes were digitized, and quantitative ultrasound measurements were made using the Indec computer system (Mountain View, CA). Approximately, three to five matched cross-sections predominantly in the left anterior descending coronary artery were studied from baseline to 1-year follow-up. IVUS cross sections were matched using identifiable landmarks in the images, such as bifurcations, artery calcification or external landmarks, such as coronary veins or the pericardium. In addition, the 1-year IVUS studies were obtained with an angiographic roadmap of where the initial IVUS study was performed along the length of the vessel. The IVUS system used was 20 MHz, and a slow manual pullback was performed at 1 mm/s from the mid-distal portion of the study vessel where an easily identifiable landmark was visible (i.e. branchpoint). The following parameters for intimal thickness were measured for each patient: maximal intimal thickness (MIT), intimal area (IA) and vessel area (VA) defined as the border of the external elastic membrane. As the media are very small, the external elastic membrane essentially outlines the measurable intima. Intimal index (II) or percent area stenosis was then calculated as IA/External Elastic Membrane. IVUS data were reviewed to determine the delta change (comparing baseline to 1 year) in intimal thickness. This method accounted for preexisting donor coronary artery disease in the dataset.

The largest change in MIT in any matched site (from baseline to 1 year) was used for each patient. The percentage of patients in each group (MMF vs. AZA groups) with change in MIT $\geq$ 0.3, 0.4 and 0.5 mm were assessed. The mean MIT for each patient was calculated (averaging all MITs from matched sites in each patient) and averaged for a group mean MIT. The IVUS reviewers were blinded to the randomization of study medications for all patients.

Statistical Analysis

Summary statistics on demographic and IVUS data between groups were calculated and compared. Data are presented as mean $\pm$ standard deviations or as proportions (percentages) of total counts. Differences in continuous means were compared using separate variance *t*-tests (Satterthwaite's approximation), and differences in proportions were compared using Fisher's exact tests (visual inspection of normal probability plots for continuous IVUS factors did not indicate that normality assumptions were unjustified). All tests were two-sided with a statistically significant p-value defined as less than 0.05. Data analysis was performed using STATA statistical software (Stata Corporation, College Station, TX).

Results

There was no significant difference in baseline characteristics between the AZA and MMF groups (Table 1). Baseline MIT was similar in the AZA and MMF groups (0.39 $\pm$ 0.39 mm vs 0.39 $\pm$ 0.37 mm).

The percentage of patients with a first-year change in MIT $\geq$0.3 was significantly greater in the AZA-treated group compared to the MMF-treated group (Table 2). Numerically, more AZA-treated patients had a first-year change in MIT of $\geq$0.4 and 0.5 mm compared to the MMF-treated patients; however, this did not reach statistical significance ($p = 0.05$ and 0.10, respectively, Table 2). The first-year change in group mean MIT was greater for the AZA group compared to the MMF group (0.29 $\pm$ 0.30 mm vs. 0.21 $\pm$ 0.25 mm, $p = 0.05$). First-year decrease in the mean lumen area in the AZA group was significantly greater compared to the MMF group ($p = 0.02$, Table 3). Finally, at 1 year, the mean vessel area decreased in the AZA group and actually increased in the MMF group ($p = 0.03$, Table 3). No significant difference was found between groups in first-year change in IA or II (Table 3).

All IVUS measurements were performed by two skilled operators who were blinded to medication randomization. The intraobserver variability in terms of percentage for the lumen area was 0.08 $\pm$ 2.1% and the intraobserver

Table 1: Patient demographics of the AZA and MMF groups

	AZA (N = 91)	MMF (N = 99)
Mean age $\pm$ SD (year)	50.6 $\pm$ 10.1	52.8 $\pm$ 8.6
Male (%)	77 (85)	78 (79)
Ischemic pretransplant diagnosis (%)	41 (45)	55 (56)
CMV mismatch (%) (donor +, recipient −)	11 (12)	12 (12)
Donor age (years)	29.4 $\pm$ 13.2	27.7 $\pm$ 12.2
Mean HLA mismatch $\pm$ SD	4.6 $\pm$ 1.1	4.6 $\pm$ 1.2
Pretransplant PRA $\geq$ 10% level (%)	8 (9)	4 (4)
Mean cold ischemic time $\pm$ SD (h)	3.1 $\pm$ 0.9	3.1 $\pm$ 1.0
Pretransplant diabetes (%)	53 (58)	49 (49)
Statin therapy at 1 year (%)	42 (46)	49 (49)

Table 2: First-year change in MIT in AZA versus MMF patients

First-year change in MIT	AZA n (%)	MMF n (%)	Fisher's p-value
$\geq$0.3 mm	39 (43%)	23 (23%)	0.005
$\geq$0.4 mm	25 (27%)	15 (15%)	0.05
$\geq$0.5 mm	17 (19%)	10 (10%)	0.10

Table 3: First-year change in other IVUS parameters

		First-year change in areas and index area			
		Lumen	Vessel	Intimal (plaque)	Percent intimal index
Agent	N	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
AZA	91	−1.20 ± 2.17	−0.40 ± 1.76	0.80 ± 1.32	5.2% ± 8.5%
MMF	99	−0.48 ± 2.02	0.19 ± 2.01	0.67 ± 0.99	3.9% ± 6.2%
p-Values	–	0.02	0.03	0.44	0.23

variability for vessel area (external elastic membrane) was 0.4 ± 1.5%. The reproducibility of measurement in terms of mean interobserver variability was 1.4 ± 3.8% for lumen area and 2.7 ± 3.3% for external elastic membrane area. These variabilities are very small and should not influence the results.

Discussion

This reassessment of the IVUS data from the randomized multicenter MMF trial using site-to-site analysis demonstrates that MMF decreases the progression of intimal thickening in the first year after heart transplantation.

IVUS has been recognized as a sensitive tool to assess the anatomy of the epicardial coronary arteries, including intimal and adventitial wall thickness. The first-year IVUS results render the greatest amount of intimal thickening compared to the other early years after transplant (7). This rapid development of intimal thickening during this first year after transplant probably reflects the accumulated insults to the donor heart, which may include explosive donor brain death, recurrent low-grade cellular rejections, donor-specific antibody production (humoral rejection) and cytomegalovirus infection (8–11). Several measurements are available in the analysis of IVUS images, including lumen area, external elastic membrane area, MIT and IA. In CAV, MIT, defined as the greatest distance from the intimal leading edge to the external elastic membrane, has been shown to be a clinically useful measurement because of its high reproducibility and its use in predicting outcome in transplant recipients (2–5).

Reports have been published on IVUS data (using site-to-site image analysis) as a surrogate marker for clinical outcomes. Mehra reported that 74 heart transplant patients with severe intimal thickening (>0.5 mm) had more events (death, myocardial infarction and retransplantation) with approximately 4 years of follow-up (2). Rickenbacher reported an increased cardiac event rate in 145 patients with a mean intimal thickening of >0.3 mm. In that study, during a mean follow-up time of 48 months, patients with mean intimal thickness of greater than 0.3 mm had significantly worse 4-year overall survival (73% vs. 96%, $p = 0.005$) and cardiac survival (79% vs. 96%, $p = 0.005$) (3). Kapadia reported the impact of rapidly progressive intimal thickening (>0.5 mm increase in intimal thickening) in the first year of transplant in 100 transplant recipients (4). Over 43 months of mean follow-up, patients with first-year rapidly progressive intimal thickening had more subsequent events (death, myocardial infarction and heart failure) compared with patients with no evidence of rapidly progressive intimal thickening (25% vs. 11%).

A recent randomized, double-blind, clinical trial compared two doses of everolimus with AZA, both in combination with cyclosporine and corticosteroids in recipients of a first heart transplant (12). At 1 year, the group receiving everolimus, compared with the group receiving AZA, had fewer incidences of biopsy-proven acute rejection and less patients with MIT $\geq$ 0.5 mm from baseline to 1 year after transplantation. The IVUS protocol utilized 11 matched sites in this study.

Simirlar to everolimus, sirolimus has demonstrated efficacy in the reduction of acute allograft rejection and intimal thickening. In a randomized, multicenter, open-label study, sirolimus administered in two different dosages was compared with azathioprine, all in combination with cyclosporine and steroids in recipients of a first heart transplant (13). From baseline to 2 years after transplantation, there was less progression of MIT in the sirolimus-treated patients (azathioprine 0.9 mm, sirolimus 0.5 mm; $p = 0.0865$). Furthermore, sirolimus has been shown to slow the progression of existing CAV (14). In a single-center, open-labeled randomized trial, patients with severe CAV, defined as epicardial stenosis >50%, MIT >0.5 mm and/or severe diffuse vessel tapering, were assigned to either sirolimus ($n = 22$) or continued current immunosuppression ($n = 24$) at annual cardiac catheterization. Achievement of the primary endpoint, defined as death, need for angioplasty or bypass surgery, myocardial infarction and a >25% worsening of the catheterization score, was significantly less in the sirolimus group compared to the control group (13.6% vs. 58.3%, $p < 0.001$).

To validate the use of first-year IVUS as a marker for long-term outcome, 125 cardiac transplant patients from five institutions (transplanted prior to 1997) and subsequent 5-year clinical data follow-up were reviewed (15). IVUS tapes (at baseline and 1 year) were reanalyzed at a core IVUS laboratory (University of California at Los Angeles). The change in MIT from baseline to year 1 was recorded for three matched sites in the same coronary artery. Patients with MIT $\geq$ 0.5 mm in any matched site compared

to those with MIT < 0.5 mm had a higher incidence of death or graft loss (D/GL, 20.8% vs. 5.9%, p = 0.007), had more nonfatal major adverse cardiac events and/or D/GL (45.8% vs. 16.8%, p = 0.003) and had more findings of newly occurring angiographic luminal irregularities (65.2% vs. 32.6%, p = 0.004). This multicenter study suggests that progression of intimal thickening ≥0.5 mm in the first year after transplant appears to be a surrogate marker for subsequent mortality, nonfatal major adverse cardiac events and the development of angiographic CAV through 5-years after heart transplantation. The reassessment of the IVUS data of the randomized multicenter MMF trial using the more meaningful site-to-site analysis suggests that MMF does significantly slow the progression of intimal thickening during the first year after transplant and therefore, may have long-term outcome benefits.

There was consistency in the current study's first-year IVUS results for the MMF-treated patients compared to the AZA-treated patients to develop less CAV. Compared to the AZA-treated patients, the MMF-treated patients were significantly less likely to develop MIT >0.3 mm, have less shrinkage in lumen area and vessel area (MMF with slight increase in vessel area) and have a numerically lower first-year change in IA and II (there was not a significant difference most likely due to small sample size).

The 3-year follow-up of this multicenter study has been recently reported (16). Graft survival continued to be significantly higher in the MMF group compared to the AZA group (88.2% vs. 81.7%, p < 0.01). In contrast to the first-year IVUS results on lumen diameter, quantitative coronary angiography showed no difference in coronary arterial segment diameter between the two groups. There was shrinkage in both groups that was not significantly different between the MMF and AZA groups. This indicates that constrictive remodeling of the coronary vessels, perhaps due to injury as well as vascular remodeling posttransplant, affected both groups similarly. Among evaluable treated patients, 15 of 120 AZA and 9 of 133 MMF patients (12.5% vs. 6.8%, respectively; p = 0.246) had angiographic new disease or progression of established vasculopathy at 3 years. With respect to IVUS, there was also no difference in lumen area between groups, but there was a trend toward a reduction in mean MIT in the MMF group compared to the AZA group (assessed by morphometric analysis as in the 1-year study). However, the number of patients who had complete sets of IVUS at baseline and 3 years was only 20% for each group (60 in the azathioprine group and 53 in the MMF group out of a total of 289 patients in each group). This smaller subset of patients may not be representative of the entire study population in that patients with the most severe coronary disease would have been most likely to die and not reach the 3-year IVUS end point. Therefore, as a result of the smaller numbers of patients and probable selection bias, reassessment with site-to-site analysis was not performed in this 3-year IVUS data. From previous IVUS studies (15), it appears that longer follow-up (5 years) will be necessary to demonstrate a difference in angiographic CAV as the number of patients with CAV at 3 years is small.

The exact mechanism for MMF's beneficial effect in decreasing the development of CAV may be due to the antiproliferative effects of MMF to suppress both T- and B-lymphocyte function and to control arterial smooth muscle cell migration and proliferation (17,18). MMF has been reported to reduce B-lymphocyte responses, as patients treated with this agent developed lower antivimentin antibody titers, and this was correlated with the lower incidence of CAV by IVUS (19). In addition, MMF has been reported to reduce the B-lymphocyte count, downregulate activation markers on B-lymphocytes and decrease activation of T-lymphocytes and HLA-DR-expressing natural killer cells (20). MMF has also been reported to decrease systemic inflammatory activity in heart transplant patients as indicated by reduced levels of high-sensitive C-reactive protein (21). Clinically, these added immunosuppressive effects have been reflected in significantly less rejection in the MMF-treated patients compared to the AZA-treated patients in the randomized multicenter MMF trial (1).

The major limitations of this study are the small sample size and the failure to document a difference between the groups when using the widely accepted 0.5-mm cutoff. In this current study, there was no significant difference between the groups for patients developing MIT > 0.5 mm, which is generally considered to be a more robust predictor of adverse outcomes (2, 4,14,15). While this may be due to the small number of patients developing this degree of intimal thickening, it may represent a true lack of difference between the two groups. The current study showed outcomes differences in patients with first-year MIT > 0.3 mm. While it has been reported by Richenbacker (3) in a single-center study that patients with intimal thickening >0.3 mm have significantly worse 4-year overall and cardiac survival, that is the only other published study that utilized 0.3 mm. Aside from the MIT issue, the current study shows that the effects of MMF were beneficial on lumen and vessel areas, but not on intimal plaque area or II. In contrast, both everolimus (12) and sirolimus (13) showed concordant benefits for all IVUS parameters including intimal plaque area and II. An additional confounding variable was that at the time the study was performed, only about 40% of patients were on statins, as opposed to the majority of patients in the more recent everolimus trial. While speculative in nature, as the reported beneficial effect on intimal thickness of statins is based on a single-center study (22), a higher rate of use of statins, as is now routine in the modern era, could have potentially decreased the degree of the beneficial effect seen with MMF in this study. Lastly, lack of a sustained effect after the first year by either IVUS or quantitative coronary angiography (QCA) represents an additional limitation to the current study.

In conclusion, MMF appears to slow the rapid progression in first-year intimal thickening in heart transplant patients. This benefit is consistent with the results of the randomized multicenter trial where MMF compared to azathioprine demonstrated first-year outcome benefits in increased survival and reduced rejection.

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