A Prospective, Randomized Trial of Single versus Dual Drug Immunosuppression in Heart Transplantation: The Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) Trial

Running Title: Baran et al: The TICTAC Trial

David A. Baran, MD
Mark J. Zucker, MD, JD
Luis H. Arroyo, MD
Margarita Camacho, MD
Marc E. Goldschmidt, MD
Stephen J. Nicholls, MBBS, PhD
Jeanne Prevost-Fernandez
Candace Carr, RN
Laura Adams, RN
Susan Pardi, NP
Vera Hou, NP
Maria Binetti, NP
Jeanine McCahill, NP
Joanne Chichetti, DNP, APN
Valerie Viloria, RN
Mary Gladys SanAgustin, RN
Jennifer Ebuenga-Smith, RN
Leslie Mele, RN
Anthony Martin, APRN
Donna Blicharz, RN
Kathy Wolski, MPH
Ludmilla Olesnicky, MD
Fang Qian, MD
Alan L. Gass, MD
Marc Cohen, MD

1- Newark Beth Israel Medical Center, Newark, NJ
2- Cleveland Clinic, Cleveland, Ohio
3- Westchester Medical Center, Valhalla, NY

Correspondence to
David A. Baran, MD, FACC
Director, Heart Failure and Transplant Research
Newark Beth Israel Medical Center, Newark, NJ
Clinical Associate Professor of Medicine, New Jersey Medical School
Telephone: (973) 926-7205, Fax: 973-926-2640
Email: dbaran@sbhcs.com

Journal Subject Codes: [37] CV surgery: transplantation, ventricular assistance, cardiomyopathy
Abstract

Background—Cardiac transplantation, a procedure nearly abandoned in the 1970’s, has evolved into the standard of care for appropriate patients with end stage heart failure. Much of this success has been due to improvements in immunosuppression, including the introduction of a triple-drug regimen. Retrospective reports suggested that single drug immunosuppression with tacrolimus was feasible. As such, a prospective randomized trial was conducted to test this approach.

Methods and Results—150 adult de novo heart transplant recipients were enrolled in a prospective, randomized, controlled, open-label trial comparing tacrolimus monotherapy (MONO) with tacrolimus and mycophenolate mofetil therapy (COMBO). Corticosteroids were used in the early post-operative period but discontinued in all patients over 8-9 weeks. The primary endpoint was the composite biopsy score at 6 months post-transplant. Patients were followed for 1-5 years. The composite biopsy score was similar between groups at 6 and 12 months: 6 month MONO 0.70 ± 0.44 (95 % CI 0.60 - 0.80) vs. COMBO 0.65 ± 0.40 (95 % CI 0.55- 0.74) (p=0.44). Allograft vasculopathy was assessed by angiography and intravascular ultrasound, with no significant differences noted. Three year survival was also similar (92.4% MONO vs. 97% COMBO (p=0.58, log-rank).

Conclusions—Addition of mycophenolate to single agent immunosuppression did not provide an advantage over single agent immunosuppression in terms of rejection, allograft vasculopathy, or 3-year survival. Corticosteroids, which have traditionally been a mainstay of therapy, were successfully discontinued in all patients. These conclusions are tempered by the limited statistical power associated with a sample size of only 150 patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov, Unique identifier: NCT00299221.

Key Words: immunosuppression transplantation; orthotopic heart transplant; randomized controlled trial; transplantation; intravascular ultrasound
Cardiac transplantation, a procedure nearly abandoned in the 1970’s\textsuperscript{1,2} has evolved into the standard of care for appropriate patients with end stage heart failure. Much of this success can be attributed to the introduction of cyclosporine A in 1980 which, in combination with corticosteroids and azathioprine, resulted in one year graft and patient survival of greater than 80\%.\textsuperscript{3} There has been little effort over the past 25 years to modify the standard triple-drug immunosuppression regimen. Efforts have focused on substituting tacrolimus (TAC) for cyclosporine\textsuperscript{4,5}, mycophenolate mofetil (MMF) for azathioprine\textsuperscript{6}, or adding a 4\textsuperscript{th} agent to the regimen\textsuperscript{7,8}.

Retrospective reports of heart transplant patients treated with TAC as monotherapy (following a short course of corticosteroids) have shown low rates of allograft rejection and excellent survival.\textsuperscript{9,10} These encouraging data prompted a prospective, randomized trial of de novo heart transplant recipients treated with TAC monotherapy versus TAC/MMF treatment, following a very short period of corticosteroid therapy. The interim results have been published previously\textsuperscript{11}, and now the median 3 year follow-up is described. It was the hypothesis of the study that heart transplant recipients treated with TAC monotherapy would accrue a similar composite rejection score as recipients treated with TAC / MMF combination therapy.

**Methods**

This was a prospective, randomized, controlled, open-label trial with two study groups. All patients received oral TAC along with MMF and corticosteroids for the first 2 weeks post-transplantation. Subsequently, study patients were randomized to either the “COMBO” group in which MMF was maintained (in the absence of limiting side-effects), or the “MONO” group in
which MMF was discontinued between 14 and 28 days post-operatively. Randomization for both study sites was via a sequential series of sealed opaque envelopes each containing a treatment assignment. Envelopes were prepared in blocks of 25 patients, 13 MONO and 12 COMBO assignments each. This led to a total of 4 extra patients in the MONO group. The study was approved by the Institutional Review Boards of both study sites and was registered with ClinicalTrials.gov (NCT00299221).

Eligible study patients were those adults able to provide informed consent who were undergoing an isolated first heart transplant. Exclusion criteria included ventilator-dependence through 14 days post-transplant (n=10), antibody mediated (humoral) rejection in the first 14 days after transplant (n=3), intolerance to TAC (n=2), refusal / inability to provide informed consent (n=3). From April 2004 through September 2008, 150 adult patients at two centers were enrolled, as detailed on Figure 1.

The primary endpoint of the trial was the mean cumulative International Society for Heart and Lung Transplantation (ISHLT) biopsy score over the first 6 months post-transplantation. Pre-specified secondary endpoints were all-cause mortality, incidence of ISHLT grade 2R/3R rejection over 6 and 12 months, one year mean cumulative ISHLT biopsy score, and the incidence of allograft vasculopathy.

**International Society for Heart and Lung Transplantation Biopsy Score**
This scale assigns a numeric value to the grades of allograft rejection according to the older formulation of the ISHLT. Biopsy grades 0, 1A, 1B, 2, 3A, 3B, and 4 are assigned to numerical values 0, 1, 2, 3, 4, 5, and 6 respectively. Prior investigators have utilized this scale in other heart transplant studies. More recently, the ISHLT has revised the grading scheme to include 0R (former 0), 1R (including former 1A, 1B and 2), 2R (3A), and 3R (3B and 4).

There were 2 pathologists primarily responsible for interpreting biopsies during the study, and they were blinded to treatment assignments. A set of biopsies of each pathologic grade were re-reviewed in a blinded fashion by both pathologists. The agreement between the original reported biopsy grade and the repeat evaluation was 86.5 % - 92 % for the two pathologists.

**Immunosuppressant Dosing**

Oral TAC was given to achieve target levels of 8-10 ng/dl within the first 7-10 days post-transplant. MMF was started at 500-1000 mg twice daily, adjusted according to labs and side effects. Methylprednisolone 500 mg was given pre-operatively and intra-operatively, followed by 125 mg intravenously every eight hours times three followed by two doses of 40 mg (every 12 hours). After this, oral prednisone was begun at 0.6 mg/kg daily (or intravenous methylprednisolone equivalent). Other than a single patient receiving one dose of rabbit anti-thymocyte globulin, induction therapy was not used.

Long-term TAC trough levels were targeted at 8-10 ng/dl, as a guideline for all patients. Likewise, the MMF dose target was 2000 mg per day, if tolerated clinically.
Prednisone was discontinued over 8 weeks post-transplant by means of a weekly weaning protocol, beginning with a dose of 0.6 mg/kg prednisone during the first post-transplant week. The dose was decreased by 0.1 mg/kg/day each week and steroids were discontinued by 8 weeks post-transplant.

During the first 3 post-transplant months only, ISHLT 1R (old grade 2, but not 1A or 1B) and asymptomatic ISHLT grade 2R rejection was treated with oral prednisone at 1 mg/kg/day for 3 days. Patients with grade 3R or symptomatic lesser grade rejection were hospitalized and were treated with methylprednisolone 500 mg intravenously on the first day and then 100-250 mg daily for 2 subsequent days. For all rejection episodes, biopsies were repeated within two weeks. No patient required anti-lymphocyte antibody treatments. CMV and pneumocystis carinii prophylaxis was given in all patients, regardless of pre-transplant CMV antibody status as described previously.11

Coronary angiography was routinely performed within 3-6 months post-transplant, and at yearly intervals thereafter. Starting in 2005, IVUS was utilized at the time of surveillance angiography when technically feasible. Typically IVUS was performed during the first 2-6 months post-transplant and at the annual evaluation. The Boston Scientific Galaxy system and Atlantis Pro SR 40 Mhz IVUS catheter were utilized with motorized automated pullback for all studies. Typically the left anterior descending coronary artery was imaged, after pre-treatment with intracoronary nitroglycerin. Studies were archived on digital discs for core lab analysis.
The core lab was blinded to study group assignments and measured multiple parameters for each IVUS examination. When possible, individual patient studies were matched based on anatomic landmarks, allowing precise quantitation of progression of atheroma formation at identical sites over time. In some cases, the core lab was unable to precisely match baseline and followup studies based on the presence of anatomic landmarks. Parameters reported include average plaque area, average lumen area, average maximal intimal thickness, largest intimal thickness, and percent atheroma volume. In addition, the changes in these parameters from baseline to follow-up examination were also calculated.

**Statistical Analysis**

All patient data was examined according to the intention-to-treat principle. The mean ISHLT biopsy scores were calculated for both groups at 6 and 12 months and compared using t-tests. Survival or freedom from rejection was quantitated with Kaplan-Meier curves and comparisons made by log-rank test. Biopsies during the first 14 days post-transplant when all patients received identical therapy were not analyzed. IVUS parameters were compared by t-tests. In all cases, two-tailed p<0.05 was considered significant. Analyses were done utilizing JMP 7 software (SAS Institute, Cary, NC).

The power calculations utilized in the design of this trial were based on earlier reports which described the ISHLT biopsy score. The estimates of average biopsy score and standard deviation were 1.0 ± 0.4 and 1.5 ± 0.6 in respective reports by Mehra and Yamani et al.
Using JMP 7 software, Design of Experiments Module, the following parameters were specified: Alpha 0.05, the difference to detect between mean biopsy scores as 0.2, and standard deviation of error as 0.4. This equated to an 86% power to detect such a difference with 150 patients.

**Results**

From April 2004 through September 2008, 150 adult patients were enrolled. The demographics of this group are detailed in Table 1. There were no significant differences between groups in regard to age, gender, racial group, pre-transplant diabetes mellitus, incidence of significant allosensitization, use of a pre-transplant ventricular assist device, or United Network for Organ Sharing (UNOS) status prior to transplantation.

There were 79 patients in the MONO group and 71 in the COMBO group, and the follow-up is reported for a median of 3 years (range 1-5 years). The primary endpoint of the trial was the 6 month mean ISHLT biopsy score. The 6 month mean biopsy score was 0.70 ± 0.44 (95% CI 0.60 - 0.80) in the MONO group and 0.65 ± 0.40 (95% CI 0.55 - 0.74) in the COMBO group (p=0.44). The 12 month mean biopsy score was 0.67 ± 0.39 (95% CI 0.59 - 0.76) in the MONO group and 0.62 ± 0.39 (95% CI 0.53 - 0.71) in the COMBO group (p=0.38). Table 2 lists the biopsy results for 6 and 12 months post-transplant. The majority of the biopsies were negative or low-grade (0R-1R).

The observed mean biopsy scores were lower than the average biopsy scores reported by others, leading to significant alterations in the achieved statistical power. Using StudySize 2.0 software
(CreoStat HB), the following parameters were entered: Alpha 0.05, standard deviation of error 0.42, sample size 150, equivalence limit 0.1. The achieved power to detect a difference of 0.2 in biopsy score was 0.15 (15 %) based on these parameters. However, achieving 80 % statistical power with the same parameters would require a sample size of 1750 patients, which would be challenging in the arena of cardiac transplantation. This rendered the trial quite underpowered in terms of the primary endpoint, and justified the long-term surveillance for other hard outcomes such as allograft vasculopathy and all-cause mortality.

Twelve month freedom from allograft rejection ≥ ISHLT grade 2R is presented in Figure 2, Panel A. The freedom from rejection ≥ ISHLT grade 2R at 6 months was 85.9 % and 94.4 % in the MONO and COMBO groups, respectively (p=0.14 log-rank). At 12 months the freedom from rejection was 85.9 % and 93.1 % in the MONO and COMBO groups, respectively (p=0.14 log-rank). Several patients experienced more than one rejection of at least ISHLT grade 2R (3 MONO and 3 COMBO patients). No rejection occurred in the MONO group after 120 days, and a single COMBO patient experienced rejection between 180 and 210 days.

Antibody-mediated rejection occurred in 2 patients (one MONO and one COMBO), both within the first 90 days post transplant. Both patients responded to a 4 day course of intravenous immune globulin (total dose 2 grams / kg over 4 days), with no recurrence.

The freedom from any treated rejection (defined as any use of oral or intravenous steroids) is displayed in Figure 2, Panel B. The freedom from treated rejection was 74.4 % and 81.9 % in the
MONO and COMBO groups, respectively at 6 months and 70.5% and 80.6% in the MONO and COMBO groups, respectively at 12 months (p=0.15 log-rank).

Patients were allowed to cross-over treatment assignments at the discretion of the investigators in this open-label trial. There were 9/79 patients who changed from a MONO to a COMBO treatment strategy due to the occurrence of rejection. The trial protocol allowed clinical judgment to drive the decision to add MMF to a MONO patient. None of the 9 patients had severe graft dysfunction or hemodynamic compromise. None of these patients experienced recurrent rejection after addition of MMF. There were 26/71 COMBO patients who were withdrawn from MMF therapy (usually due to neutropenia unresponsive to MMF dose reduction). Patients who discontinued MMF remained on TAC monotherapy. Two of these patients experienced a single episode of grade 2R asymptomatic rejection, which was treated with oral corticosteroids for 3 days. No patient required addition of alternate chronic immunosuppressants, including maintenance corticosteroids. All analyses are by intention-to-treat.

The effect of MMF discontinuation (group crossover) is explored in Figure 2, Panel C. Depicted is the freedom from rejection based on the treatment received. The COMBO group is divided into those patients who receive MMF for at least 6 months, versus those who discontinue the assigned therapy for intolerance prior to this time post-transplant. While there is no statistically significant difference, the group with the highest freedom from rejection is those randomized to COMBO who receive MMF for at least 6 months.
Freedom from allograft vasculopathy, as assessed by coronary angiography, is shown in Figure 3. Vasculopathy was defined as a 50% or greater luminal stenosis in any vessel (excluding donor-transmitted disease noted on angiography within 3 months post-transplant). The angiographic freedom from disease in the MONO group was 100%, 96%, and 96% at 1, 3, and 5 years post-transplantation. In the COMBO group the freedom was 100%, 98.4%, and 98.4% (p=0.34 MONO vs. COMBO). Diseased segments of at least 70% stenosis were treated with percutaneous coronary intervention, typically with a drug-eluting stent. Due to small sample size, and the insensitivity of angiography to detect allograft vasculopathy, it is not possible to rule out a difference between groups.

IVUS was performed in 138 of 150 patients. Of these, 113 / 138 patients had data which was technically adequate for core lab analysis. Since IVUS was not available at all points during the study, not all patients had a baseline examination within 6 months post-transplant as well as a follow-up study. Baseline (prior to 6 months post-transplant) and follow-up data was available for 42 patients and this subset was analyzed separately in addition to the overall 113 patient IVUS data. The analysis of the 113 patient cohort showed no significant differences in any parameter studied, although there was a consistent trend towards less plaque, less progression of intimal thickening, and less progression of percent atheroma volume in the MONO group.

Table 3 shows the analysis of the 42 patients with paired baseline (prior to 6 months post-transplant) and follow-up data. The best studied IVUS parameter in heart transplant recipients is the average maximal intimal thickness. It has been shown that a change of at least 0.5 mm between early post-transplant baseline and a 1 year IVUS study is associated with excess risk of
death and development of allograft coronary artery disease.\textsuperscript{18} In the 42 patients with matched IVUS studies, none of the 22 MONO patients had growth of intimal thickness of 0.5 mm or more, but 2 of the 20 COMBO patients did (\textit{p}=0.08). Most of the Core Lab measured indices did not show statistically significant differences between groups. Only the change in percent atheroma volume was of borderline statistical significance in favor of the MONO group with 1.78 \pm 5.62 \% change in MONO and 6.83 \pm 10.46 \% change in the COMBO group.

All-cause mortality is presented as a Kaplan-Meier plot in Figure 4. Survival in the MONO group was 97.5\%, 92.4\% and 87.2\% at 1, 3, and 5 years respectively. Survival in the COMBO patients was 98.6\%, 97 \%, and 90.6 \% at 1, 3, and 5 years respectively (\textit{p}=0.58, log-rank). The survival analysis was repeated for the “on-treatment” cohort of patients who did not cross-over treatment assignment and was similar, with no significant differences noted (\textit{p}=0.34). It is important to note that survival between groups was not identical, and given the low sample size (150 patients), no definitive conclusion may be reached in regards to this severely underpowered secondary endpoint.

There were 20 episodes of infection requiring treatment noted in the MONO group and 25 in the COMBO group (\textit{p}=0.5). Opportunistic infections were rare, with 4 patients treated for cytomegalovirus disease (2 MONO and 2 COMBO patients), which resolved with therapy. There were no cases of \textit{pneumocystis carinii} pneumonia or toxoplasmosis with 1 year of trimethoprim / sulfamethoxazole prophylaxis.
Table 4 lists the white blood cell count, blood urea nitrogen, serum creatinine and tacrolimus levels for the patients in the study at baseline, 6, 9 and 12 months post-transplant. While the values are similar at the time of transplant, the mean white blood cell count is statistically significantly less at 6 months in COMBO patients (but not in a clinically meaningful degree). The renal function at 6 months was lower for the MONO group, but was no longer significant at 9 months and of borderline significance at 12 months. Long-term follow-up is planned to monitor renal function over time. Tacrolimus levels were not different between groups at any time interval.

**Discussion**

For nearly 30 years, heart transplant patients have been treated with “triple therapy” consisting of a calcineurin antagonist, a cell-cycle modulating drug and corticosteroids. While several trials have examined substitutes for one of the components of the combination, TAC monotherapy has never been prospectively studied before.

The TICTAC trial primarily addresses the safety and comparative efficacy of TAC monotherapy versus TAC / MMF following a brief course of steroids post-transplant. Patients in both groups were successfully weaned from steroids, and the 3 year median follow-up results are encouraging in terms of rejection, vasculopathy and mortality. These three aspects are all linked, as acute cellular rejection is believed to predispose to the development of allograft vasculopathy, which is one of the leading causes of mortality in heart transplant patients.
One of the most critical aspects to consider is the patient selection for this trial. 18 patients transplanted during the trial enrollment period were excluded. The survival of all patient groups is depicted in Figure 4, Panel B. The excluded patients included 10 whom were ventilator dependent during the first 14 days post transplant (6 month and 1 year survival of 20 %, and 0 % respectively), as well as 5 patients who either declined participation in the trial or who had intolerance to tacrolimus (100 % survival at 1 year post-transplant), and 3 patients with antibody mediated rejection within 14 days of transplantation (66.7 % survival at 6 and 12 months post-transplant). It is not likely that any immunosuppressive strategy would improve outcomes in the 10 patients who could not be weaned from the ventilator post-transplant, and therefore their exclusion does not detract significantly from the utility of the results observed in this trial. None of these patients experienced allograft rejection (cellular or antibody mediated) during the first month post-transplant. Patients with early (within the first 14 days only) antibody mediated rejection also represent a small but high-risk group and it was not felt to be ethical to potentially randomize such patients to single drug therapy. However, AMR did occur in two patients who were followed in the trial, both of whom were successfully treated and maintained in the study.

These results compare favorably to prior studies with more traditional immunosuppression. Although some centers do wean “low-risk” patients from corticosteroids typically beginning 6 months post-transplantation, the 2009 ISHLT registry data reveals that 71% of patients still remain on steroids 1 year post-transplant. An alternative approach is therapy with induction antibody preparations, such as rabbit anti-thymocyte globulin or alemtuzumab to “facilitate” steroid withdrawal. None of these studies report less rejection or improved mortality as compared to the current study’s findings. While other studies have examined late steroid
weaning, and not found significant success\textsuperscript{25, 26}, this is the first prospective study to specifically mandate a rapid weaning schedule based on patient weight. It is important to emphasize that this trial did not have a group which received chronic steroid therapy, and therefore, did not directly compare the outcomes of traditional steroid maintenance and rapid steroid weaning. A prospective, randomized trial comparing traditional steroid weaning by 6-12 months versus 8 week weaning is currently in the planning stages.

The current study integrates IVUS, but not as part of the primary endpoint, since it was not in routine use at study sites in 2004. Nevertheless, 138 of 150 patients had at least one IVUS study, and these were analyzed by the Cleveland Clinic IVUS Core Lab, which was not involved in the conduct of the study. The Core Lab conducted analyses of matched sites by comparing anatomic landmarks on the studies. Multiple parameters were measured by the Core Lab including percent atheroma volume (PAV) which has been utilized in a number of recent clinical trials in atherosclerosis.\textsuperscript{27-30} There were 113 patients with studies analyzed by the Core Lab, with the finding of similar degrees of lumen shrinkage, and plaque growth, over varying periods of time post-transplant. While the data is most robust when examining paired patient studies, there is utility to examining the full available dataset, to exclude a signal of harm associated with single drug therapy.

Nearly a third of the patients in the trial had an early baseline IVUS and a matching follow-up study, with results presented in Table 3. Previous studies such as Eisen et. al.\textsuperscript{20} have also obtained IVUS studies in approximately a third of patients (211 of 634 patients, 33\%). There were no statistically significant differences, except for a strong trend towards a smaller change in
PAV in the MONO vs. COMBO group (p=0.055). There were non-significant trends towards less lumen shrinkage, less intimal thickening, and less atheroma in the MONO group.

Despite the advantages of IVUS, angiography remains the most commonly utilized modality to assess allograft vasculopathy. ISHLT Registry data report that 20 % of patients will have angiographically apparent disease by 3 years, rising to 30 % at 5 years. While the numbers of patients in this study was relatively small, the incidence of allograft vasculopathy was less than 5 % in both groups with a median 3 year follow-up period. Taken together, these results indicate that there is no significant disadvantage to TAC monotherapy and there may be a benefit of less medication.

It is notable that survival was similar between groups with less than 3% mortality during the first year post-transplant, although the trial was underpowered to assess this endpoint, and excluded the patients who remained ventilator dependent post-transplant. Registry data consistently show that the largest declines in post-transplant survival occur during the first year. These findings suggest a new direction for future trials in cardiac transplantation. Perhaps efforts should be directed towards reducing immunosuppression, and identification of surrogate markers which would allow safe and effective minimization of these toxic but life-saving drugs.

The fact that less immunosuppression is associated with a very low risk of rejection is counter-intuitive and unexpected. One theory is that the low TAC levels during the first week post-transplant may provide a Window of Opportunity for Immunologic Engagement (WOFIE) which
may enhance the production of T-regulatory cells. This is speculative at best and the current study provides no mechanistic insight into the clinical outcomes observed.

**Limitations**

The most important limitation of this work is that it is underpowered. The event rates garnered from the literature which were used in the power calculations were much higher than those observed in this study. Therefore, no concrete assessment may be made as to the equivalence of the two study groups. Similarly, the trial is not appropriately powered to assess mortality and the IVUS analyses are limited by the lack of consistent baseline and follow-up studies. In addition, this study is not applicable to those patients with AMR in the first 14 days post-transplant, or patients remaining ventilator-dependent during the same period. These limitations are partially counter-balanced by a median 3 year follow-up, along with independent core lab analysis of the IVUS data using the latest and most sensitive IVUS analysis techniques.

The questions of whether, when, and in whom single immunosuppression might be considered clearly warrant re-examination and further investigation. Clearly, patient compliance and the ability of the transplant team to closely monitor these patients and coordinate their care is critical to successful outcomes. Nevertheless, these findings may be most reassuring to clinicians who are faced with the need to rapidly reduce immunosuppression due to not infrequent problems such as intolerance to MMF or severe infections in the early months post-transplant when these data may be applicable.

**Conclusion**
The TICTAC trial is the first prospective test of single versus dual drug maintenance immunosuppression in heart transplantation. Steroid weaning was successful in all study patients, and should be considered a potential option for heart transplant patients who can be monitored closely during the weaning process. The excellent 3-year survival and low rates of allograft rejection and vasculopathy observed in both arms of this study support the efficacy of either TAC monotherapy or TAC / MMF along with a brief course of corticosteroids post-transplantation.
Sources of Funding

This trial was partially supported by two investigator-initiated grants from Astellas Pharmaceuticals which covered enrollment of the first 50 patients, and the core lab analysis of intravascular ultrasound data. The database was designed and maintained by the authors who had full access to the data. There was no involvement of Astellas in the design, writing, or decision to submit the paper.
Disclosures

David A Baran:
Research Grant: Astellas Pharma, Amount: $10,000
Honoraria: Astellas, Amount: < $10,000
Expert Witness: Unpaid voluntary testimony at Medicaid of New Jersey Generic Substitution committee

Mark Jay Zucker:
Research Grant: Astellas, Amount: $10,000

Luis H Arroyo: No disclosures

Margarita Camacho:
Research Grant: Astellas, Amount: $10,000

Marc E Goldschmidt:
Research Grant: Astellas, Amount: $10,000

Stephen James Nicholls:
Research Grant: Astellas Pharma grant for IVUS Core Lab Analysis, Amount: $10,000

Jeanne Prevost-Fernandez: No disclosures

Candace Carr: No disclosures

Laura Adams: No disclosures

Susan Pardi: No disclosures

Vera Hou: No disclosures

Maria Binetti: No disclosures

Jeanine McCahill: No disclosures
JoAnne Chichetti: No disclosures

Valerie Viloria: No disclosures

Mary Gladys SanAgustin: No disclosures

Jennifer Ebuenga-Smith: No disclosures

Leslie Mele: No disclosures

Anthony Martin: No disclosures

Donna Blicharz: No disclosures

Kathy Wolski:

Research Grant: Astellas Pharma grant to support statistical review of trial data, Amount: $10,000

Ludmilla Olesnicky: No disclosures

Fang Qian: No disclosures

Alan L Gass:

Research Grant: Astellas Pharma- Support for TICTAC trial enrollment, Amount: < $10,000

Honoraria: Astellas Pharma- CME lectures, Amount: < $10,000

Marc Cohen: No disclosures
References


mycophenolate mofetil (mmf) or sirolimus vs. Cyclosporine with mmf in cardiac transplant patients: 1-year report. *Am J Transplant.* 2006;6:1377-1386


27. Nicholls SJ, Tuzcu EM, Schoenhagen P, Sipahi I, Crowe T, Kapadia S, Nissen SE. Effect of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) on arterial remodeling at coronary branch points (from the reversal study). *Am J Cardiol.* 2005;96:1636-1639


Table 1. Group Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>MONO Group (n=79)</th>
<th>COMBO Group (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55 ± 10.7</td>
<td>55 ± 11.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Male Gender</td>
<td>62</td>
<td>60</td>
<td>0.40</td>
</tr>
<tr>
<td>Black Race</td>
<td>17</td>
<td>11</td>
<td>0.40</td>
</tr>
<tr>
<td>Pre-Tx DM</td>
<td>28</td>
<td>22</td>
<td>0.40</td>
</tr>
<tr>
<td>PRA ≥ 10 %</td>
<td>23</td>
<td>22</td>
<td>0.86</td>
</tr>
<tr>
<td>Pre-Tx VAD</td>
<td>21</td>
<td>19</td>
<td>0.98</td>
</tr>
<tr>
<td>High-Risk CMV</td>
<td>23 (29 %)</td>
<td>13 (18 %)</td>
<td>0.13</td>
</tr>
<tr>
<td>Donor Age</td>
<td>31.3 ± 12.8</td>
<td>31.7 ± 12.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Female Donor</td>
<td>37 (46.8 %)</td>
<td>24 (33.8 %)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cold Ischemic Time</td>
<td>198 ± 51</td>
<td>194 ± 47</td>
<td>0.59</td>
</tr>
<tr>
<td>UNOS Status 1A</td>
<td>45</td>
<td>31</td>
<td>0.15</td>
</tr>
<tr>
<td>UNOS Status 1B</td>
<td>30</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>UNOS Status 2</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Biopsy Data

<table>
<thead>
<tr>
<th></th>
<th>MONO Group</th>
<th></th>
<th>COMBO Group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Biopsies / %</td>
<td></td>
<td># Biopsies / %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>12 Months</td>
<td>6 Months</td>
<td>12 Months</td>
</tr>
<tr>
<td>Grade 0R</td>
<td>330 / 45%</td>
<td>425 / 47 %</td>
<td>315 / 47 %</td>
<td>416 / 50 %</td>
</tr>
<tr>
<td>Grade 1R (1A)</td>
<td>314 / 43%</td>
<td>381 / 42 %</td>
<td>275 / 41 %</td>
<td>330 / 40 %</td>
</tr>
<tr>
<td>Grade 1R (1B)</td>
<td>48 / 6 %</td>
<td>53 / 6 %</td>
<td>39 / 6 %</td>
<td>45 / 5 %</td>
</tr>
<tr>
<td>Grade 1R (2)</td>
<td>31 / 4 %</td>
<td>37 / 4 %</td>
<td>32 / 5 %</td>
<td>37 / 4 %</td>
</tr>
<tr>
<td>Grade 2R</td>
<td>13 / 2 %</td>
<td>13 / 1 %</td>
<td>7 / 1.0 %</td>
<td>8 / 1.0 %</td>
</tr>
<tr>
<td>Grade 3R</td>
<td>2 / 0.3 %</td>
<td>2 / 0.2 %</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>738 / 100 %</td>
<td>911 / 100 %</td>
<td>668 / 100 %</td>
<td>836 / 100 %</td>
</tr>
</tbody>
</table>
Table 3. Intravascular Ultrasound Data- Cohort with Baseline and Follow-up Exam (N=42)

<table>
<thead>
<tr>
<th>IVUS Parameter</th>
<th>Baseline Examination (≤ 180 days)</th>
<th>Follow-up Examination</th>
<th>Change- Baseline to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MONO group (N= 22)</td>
<td>COMBO group (N=20)</td>
<td>p-value (comparison Baselines)</td>
</tr>
<tr>
<td>Average Plaque Area</td>
<td>2.44 ± 0.64</td>
<td>2.73 ± 1.13</td>
<td>0.31</td>
</tr>
<tr>
<td>Average Lumen Area</td>
<td>9.71 ± 2.91</td>
<td>10.26 ± 2.87</td>
<td>0.54</td>
</tr>
<tr>
<td>Average Maximal Intimal Thickness</td>
<td>0.36 ± 0.09</td>
<td>0.39 ± 0.16</td>
<td>0.51</td>
</tr>
<tr>
<td>Largest Intimal Thickness</td>
<td>0.68 ± 0.30</td>
<td>0.71 ± 0.35</td>
<td>0.78</td>
</tr>
<tr>
<td>Percent Atheroma Volume</td>
<td>20.72 ± 5.41</td>
<td>21.02 ± 6.94</td>
<td>0.87</td>
</tr>
<tr>
<td>Average Maximal Intimal Thickness ≥ 0.5mm (# patients, % of patients)</td>
<td>1, 4.6 %</td>
<td>4, 20 %</td>
<td>0.11</td>
</tr>
<tr>
<td>Time to IVUS Exam Post-transplant</td>
<td>106.7 ± 32.6</td>
<td>113.9 ± 33.7</td>
<td>0.49</td>
</tr>
</tbody>
</table>
## Table 4. Selected Laboratory Values Post-transplant

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline at Transplant</th>
<th>6 Months Post-transplant</th>
<th>9 Months Post-transplant</th>
<th>12 Months Post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MONO</td>
<td>COMBO</td>
<td>p-value</td>
<td>MONO</td>
</tr>
<tr>
<td>White Blood Cell Count</td>
<td>9.3 ± 5.7</td>
<td>9.5 ± 5.1</td>
<td>0.81</td>
<td>5.63 ± 3.0</td>
</tr>
<tr>
<td>Blood Urea Nitrogen</td>
<td>24 ± 13.3</td>
<td>24 ± 11.8</td>
<td>0.80</td>
<td>33 ± 11.4</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>1.24 ± 0.43</td>
<td>1.26 ± 0.5</td>
<td>0.80</td>
<td>1.63 ± 0.51</td>
</tr>
<tr>
<td>Tacrolimus Level</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.8 ± 2.7</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Study Flow Diagram. This diagram illustrates flow from recruitment to study group assignment.

Figure 2, Panel A. Freedom from Allograft Rejection: 2R / 3R Rejection. This is a Kaplan-Meier plot of freedom from significant cardiac allograft rejection (ISHLT grades 2R or 3R).

Figure 2, Panel B. Freedom from Any Treated Allograft Rejection. This is a Kaplan-Meier plot of freedom from any cardiac allograft rejection which was treated. (Symptomatic or clinically suspicious rejection, even if the tissue diagnosis was negative and treatment was discontinued.)

Figure 2, Panel C. Freedom from Allograft Rejection 2R/3R. This graph examines the patients who were intolerant to MMF and their rejection outcome. Patients who did not discontinue MMF (maintained the treatment they were randomized to for at least 6 months) are compared to those who discontinue MMF within the first 6 months post-transplant, as well as all patients randomized to the MONO group.

Figure 3. Freedom from Angiographically Detected Allograft Vasculopathy. This is a Kaplan-Meier plot of the freedom from angiographically detected allograft vasculopathy. This was defined as a 50% or greater luminal stenosis in any vessel (excluding donor-transmitted disease noted on angiography within 3 months post-transplant).
Figure 4, Panel A. Survival post-transplant. This is a Kaplan Meier plot of survival post-transplant for the 150 subjects in the trial.

Figure 4, Panel B. This is a Kaplan Meier plot of survival comparing patients entered into the TICTAC trial with those excluded (based on inclusion criteria).
168 Pts Transplanted During Study Period

18 Excluded
10 Not off vent
3 Refuse / Unable to consent
3 Antibody Mediated rejection
2 Intolerance to TAC

150 Patients Enrolled

150 Patients Randomized 1:1

MONOTHERAPY
79 Pts

Cross-Over
9 Pt -> COMBO

COMBINATION
71 Pts

Cross-Over
26 Pt -> MONO

Analysis by Intention-to-Treat Principle
Circulation
Heart Failure

Freedom From Rejection

Days to First Treated Rejection

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Combo</th>
<th>Mono</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>71</td>
<td>79</td>
</tr>
<tr>
<td>64</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

p=0.18
Freedom From Allograft Vasculopathy

Years to First Significant CAD

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Combo</th>
<th>Mono</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

|       | 0     | 79   |
|       | 1     | 77   |
|       | 2     | 57   |
|       | 3     | 38   |
|       | 4     | 27   |
|       | 5     | 9    |

p = 0.34
A Prospective, Randomized Trial of Single versus Dual Drug Immunosuppression in Heart Transplantation: The Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) Trial


_Circ Heart Fail_. published online January 7, 2011;

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2011/01/07/CIRCHEARTFAILURE.110.958520