A Prospective, Randomized Trial of Single-Drug Versus Dual-Drug Immunosuppression in Heart Transplantation

The Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) Trial

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Background—Cardiac transplantation, a procedure nearly abandoned in the 1970s, 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—One hundred fifty 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 postoperative period but discontinued in all patients over 8 to 9 weeks. The primary end point was the composite biopsy score at 6 months after transplant. Patients were followed for 1 to 5 years. The composite biopsy score was similar between groups at 6 and 12 months: 6-month MONO, 0.70 ± 0.44 (95% confidence interval, 0.60 to 0.80) versus COMBO, 0.65 ± 0.40 (95% confidence interval, 0.55 to 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 versus 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. (Circ Heart Fail. 2011;4:129-137.)

Key Words: immunosuppression transplantation ■ orthotopic heart transplant ■ randomized controlled trial ■ transplantation ■ intravascular ultrasound

Cardiac transplantation, a procedure nearly abandoned in the 1970s, 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 1-year graft and patient survival of >80%. 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, mycophenolate mofetil (MMF) for azathioprine, or adding a 4th agent to the regimen.

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Retrospective reports of heart transplant patients treated with TAC as monotherapy (after a short course of corticosteroids) have shown low rates of allograft rejection and...
The interim results have been published previously,11 and treatment, after a very short period of corticosteroid therapy. Recipients treated with TAC monotherapy versus TAC/MMF according to the older formulation of the ISHLT.12,13 Biopsy grades. This scale assigns a numeric value to the grades of allograft rejection. ISHLT Biopsy Score.

**Figure 1.** Study flow diagram illustrates flow from recruitment to study group assignment.

Methods

This was a prospective, randomized trial of de novo heart transplant recipients treated with TAC monotherapy versus TAC/MMF treatment, after a very short period of corticosteroid therapy. The interim results have been published previously,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.

ISHLT Biopsy Score

This scale assigns a numeric value to the grades of allograft rejection according to the older formulation of the ISHLT.12,13 Biopsy grades 0, 1A, 1B, 2, 3A, 3B, and 4 and are assigned to numeric values 0, 1, 2, 3, 4, 5, and 6, respectively. Prior investigators have used this scale in other heart transplant studies.14,15 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).16 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 pathological grade were reviewed in a blinded fashion by both pathologists. The agreement between the original reported biopsy grade and the repeat evaluation was 86.5% to 92% for the 2 pathologists.

**Immunosuppressant Dosing**

Oral TAC was given to achieve target levels of 8 to 10 ng/dL within the first 7 to 10 days after transplant. MMF was started at 500 to 1000 mg twice daily, adjusted according to labs and side effects. Methylprednisolone 500 mg was given preoperatively and intravenously, followed by 125 mg intravenously every 8 hours 3 times followed by 2 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 1 dose of rabbit antithymocyte globulin, induction therapy was not used.

Long-term TAC trough levels were targeted at 8 to 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 after 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⁻¹ ·d⁻¹ each week and steroids were discontinued by 8 weeks after 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⁻¹ ·d⁻¹ 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 to 250 mg daily for 2 subsequent days. For all rejection episodes, biopsies were repeated within 2 weeks. No patient required antilymphocyte antibody treatments. Cytomegalovirus disease and Pneumocystis carinii prophylaxis was given in all patients, regardless of pretransplant cytomegalovirus disease antibody status as described previously.11 Coronary angiography was routinely performed within 3 to 6 months after transplant and at yearly intervals thereafter. Starting in 2005, intravascular ultrasound (IVUS) was used at the time of surveillance angiography when technically feasible. Typically, IVUS was performed during the first 2 to 6 months after transplant and at the annual evaluation. The Boston Scientific Galaxy system and Atlantis Pro SR 40-MHz IVUS catheter were used with motorized automated pullback for all studies. Typically, the left anterior descending coronary artery was imaged after pretreatment with intracoronary nitroglycerin. Studies were archived on digital discs for core laboratory analysis.

The core laboratory was blinded to study group assignments and measured multiple parameters for each IVUS examination. When possible, individual patient studies were matched on the basis of anatomic landmarks, allowing precise quantification of progression of atheroma formation at identical sites over time. In some cases, the core laboratory was unable to precisely match baseline and follow-up 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 were 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 quantified with Kaplan-Meier curves and comparisons made by log-rank test. Biopsies during the first 14 days after transplant when all patients received identical therapy were not analyzed. IVUS parameters were compared by t tests. In all
cases, 2-tailed \( P < 0.05 \) was considered significant. Analyses were done using JMP 7 software (SAS Institute, Cary, NC).

The power calculations used in the design of this trial were based on earlier reports that described the ISHLT biopsy score.\(^{17} \) The estimates of average biopsy score and standard deviation were 1.0±0.4 and 1.5±0.6 in respective reports by Mehr17 and Yamani et al.\(^{19} \) 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, sex, racial group, pretransplant diabetes mellitus, incidence of significant allosensitization, use of a pretransplant ventricular assist device, or United Network for Organ Sharing (UNOS) status before 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 to 5 years). The primary end point of the trial was the 6-month mean ISHLT biopsy score. The 6-month mean biopsy score was 0.70±0.44 (95% confidence interval, 0.60 to 0.80) in the MONO group and 0.65±0.40 (95% confidence interval, 0.55 to 0.74) in the COMBO group (\( P=0.44 \)). The 12-month mean biopsy score was 0.67±0.39 (95% confidence interval, 0.59 to 0.76) in the MONO group and 0.62±0.39 (95% confidence interval, 0.53 to 0.71) in the COMBO group (\( P=0.38 \)). Table 2 lists the biopsy results for 6 and 12 months after transplant. The majority of the biopsies were negative or low grade (0R to 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; and 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 end point 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 \( \geq 2 \)R is presented in Figure 2A. The freedom from rejection ISHLT grade \( \geq 2 \)R 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 had more than 1 rejection of ISHLT grade \( \geq 2 \)R (3 MONO and 3 COMBO patients). No rejection occurred in the MONO group after 120 days, and a single COMBO patient had rejection between 180 and 210 days.

Antibody-mediated rejection occurred in 2 patients (1 MONO and 1 COMBO), both within the first 90 days after transplant. Both patients responded to a 4-day course of intravenous immune globulin (total dose, 2 g/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 2B. 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 of 79 patients who changed from a MONO to a COMBO treatment strategy because of 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 had recurrent rejection after addition of MMF. There were 26 of 71 COMBO patients who were withdrawn from MMF therapy (usually because of neutropenia unresponsive to MMF dose reduction). Patients who discontinued MMF remained on TAC monotherapy. Two of these patients had a single episode of grade 2R asymptomatic rejection, which was treated with oral corticosteroids for 3 days. No patient required addition of alternate

### 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 sex</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 &gt;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>

\( \text{Tx} \) indicates transplant; \( \text{DM} \), diabetes mellitus; \( \text{PRA} \), panel reactive antibodies; \( \text{VAD} \), ventricular assist device; and \( \text{CMV} \), cytomegalovirus.

### Table 2. Biopsy Data

<table>
<thead>
<tr>
<th></th>
<th>MONO Group</th>
<th>COMBO Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{No. of Biopsies/%} )</td>
<td>( 6 ) Months</td>
<td>( 12 ) Months</td>
</tr>
<tr>
<td>Grade 0R</td>
<td>330/45%</td>
<td>425/47%</td>
</tr>
<tr>
<td>Grade 1R (1A)</td>
<td>314/43%</td>
<td>381/42%</td>
</tr>
<tr>
<td>Grade 1R (1B)</td>
<td>48/6%</td>
<td>53/6%</td>
</tr>
<tr>
<td>Grade 1R (2)</td>
<td>31/4%</td>
<td>37/4%</td>
</tr>
<tr>
<td>Grade 2R</td>
<td>13/2%</td>
<td>13/1%</td>
</tr>
<tr>
<td>Grade 3R</td>
<td>2/0.3%</td>
<td>2/0.2%</td>
</tr>
<tr>
<td>Total</td>
<td>738/100%</td>
<td>911/100%</td>
</tr>
</tbody>
</table>
chronic immunosuppressants, including maintenance corticosteroids. All analyses are by intention-to-treat.

The effect of MMF discontinuation (group crossover) is explored in Figure 2C. 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 after transplant. Although there is no statistically significant difference, the group with the highest freedom from rejection is those randomly assigned 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 ≥50% luminal stenosis in any vessel (excluding donor-transmitted disease noted on angiography within 3 months after transplant). The angiographic freedom from disease in the MONO group was 100%, 96%, and 96% at 1, 3, and 5 years, respectively, after transplantation. In the COMBO group, the freedom was 100%, 98.4%, and 98.4% (P=0.34 MONO versus COMBO). Diseased segments of ≥70% stenosis were treated with percutaneous coronary intervention, typically with a drug-eluting stent. Because of the 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 of 138 patients had data that were technically adequate for core laboratory analysis. Because IVUS was not available at all points during the study, not all patients had a baseline examination within 6 months after transplant as well as a follow-up study. Baseline (before 6 months after transplant) and follow-up data were 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 toward 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 (before 6 months after 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.18 In the 42 patients with matched IVUS studies, none of the 22 MONO patients had growth of intimal thickness of ≥0.5 mm, but 2 of the 20 COMBO patients did (P=0.08). Most of the core laboratory–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±5.62% change in MONO and 6.83±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 (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 (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 regarding this severely underpowered secondary end point.

There were 20 episodes of infection requiring treatment noted in the MONO group and 25 in the COMBO group (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 P 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 after transplant. Although 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

### Table 3. IVUS Data: Cohort With Baseline and Follow-Up Examinations (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>
<th>P Value (Paired t Test 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>
<td>MONO Group (n=22)</td>
</tr>
<tr>
<td>Average plaque area</td>
<td>2.44±0.64</td>
<td>2.73±1.13</td>
<td>0.31</td>
<td>2.66±0.91</td>
</tr>
<tr>
<td>Average lumen area</td>
<td>9.71±2.91</td>
<td>10.26±2.87</td>
<td>0.54</td>
<td>9.26±2.55</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>
<td>0.40±0.11</td>
</tr>
<tr>
<td>Largest intimal thickness</td>
<td>0.68±0.30</td>
<td>0.71±0.35</td>
<td>0.78</td>
<td>0.76±0.31</td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td>20.72±5.41</td>
<td>21.02±6.94</td>
<td>0.87</td>
<td>22.49±6.15</td>
</tr>
<tr>
<td>Average maximal intimal thickness ≥0.5 mm (No. of patients, % of patients)</td>
<td>1, 4.6%</td>
<td>4, 20%</td>
<td>0.11</td>
<td>5, 22.7%</td>
</tr>
<tr>
<td>Time to IVUS exam after transplant</td>
<td>106.7±32.6</td>
<td>113.9±33.7</td>
<td>0.49</td>
<td>564.5±204.5</td>
</tr>
</tbody>
</table>
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. Although several trials have examined substitutes for 1 of the components of

### Table 4. Selected Laboratory Values After Transplant

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline at Transplant</th>
<th>6 Months After Transplant</th>
<th>9 Months After Transplant</th>
<th>12 Months After 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>
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 after a brief course of steroids after 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 3 aspects are all linked, as acute cellular rejection is believed to predispose to the development of allograft vasculopathy,15,18 which is 1 of the leading causes of mortality in heart transplant patients.19

One of the most critical aspects to consider is the patient selection for this trial. Eighteen patients transplanted during the trial enrollment period were excluded. The survival of all patient groups is depicted in Figure 4B. The excluded patients included 10 who were ventilator-dependent during the first 14 days after transplant (6-month and 1-year survival of 20% and 0%, respectively), 5 patients who either declined participation in the trial or who had intolerance to tacrolimus (100% survival at 1 year after transplant), and 3 patients with antibody-mediated rejection within 14 days of transplantation (66.7% survival at 6 and 12 months after transplant). It is not likely that any immunosuppressive strategy would improve outcomes in the 10 patients who could not be weaned from the ventilator after transplant, and therefore their exclusion does not detract significantly from the utility of the results observed in this trial. None of these patients had allograft rejection (cellular or antibody mediated) during the first month after 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 thought to be ethical to potentially randomly assign such patients to single-drug therapy. However, antibody-mediated rejection did occur in 2 patients who were followed in the trial, both of whom were successfully treated and maintained in the study.

These results compare favorably with prior studies with more traditional immunosuppression.7,20,21 Although some centers do use “low-risk” patients from corticosteroids typically beginning 6 months after transplantation, the 2009 ISHLT registry data reveal that 71% of patients remain on steroids 1 year after transplant.22 An alternative approach is therapy with induction antibody preparations, such as rabbit antithymocyte globulin or alemtuzumab, to “facilitate” steroid withdrawal.23,24 None of these studies report less rejection or improved mortality as compared with the current study’s findings. Although other studies have examined late steroid weaning and did not find significant success,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 that 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 to 12 months versus 8-week weaning is currently in the planning stages.

The current study integrates IVUS, but not as part of the primary end point, because it was not in routine use at study sites in 2004. Nevertheless, 138 of 150 patients had at least 1 IVUS study, and these were analyzed by the Cleveland Clinic IVUS Core Laboratory, which was not involved in the conduct of the study. The core laboratory conducted analyses of matched sites by comparing anatomic landmarks on the studies. Multiple parameters were measured by the core laboratory including percent atheroma volume, which has been used in a number of recent clinical trials in atherosclerosis.27–30 There were 113 patients with studies analyzed by the core laboratory, with the finding of similar degrees of lumen shrinkage and plaque growth over varying periods of time after transplant. Although the data are most robust when examining paired patient studies, there is utility to examining the full available data set 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 al20 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 toward a smaller change in percent atheroma volume in the MONO versus COMBO group (P=0.055). There were nonsignificant trends toward less lumen shrinkage, less intimal thickening, and less atheroma in the MONO group.

Despite the advantages of IVUS, angiography remains the most commonly used 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.22 Although the numbers of patients in this study was relatively small, the incidence of allograft vasculopathy was <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 <3% mortality during the first year after transplant, although the trial was underpowered to assess this end point and excluded the patients who remained ventilator-dependent after 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 toward 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 counterintuitive and unexpected. One theory is that the low TAC levels during the first week after transplant may provide a Window of Opportunity for Immunologic Engagement (WOFIE), which may enhance the production of T-regulatory cells.31 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 that were used in the power calculations were much higher than those observed in this study. Therefore, no concrete
assessments may be made as to the equivalence of the 2 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 antibody-mediated rejection in the first 14 days after transplant or patients remaining ventilator-dependent during the same period. These limitations are partially counterbalanced by a median 3-year follow-up, along with independent core laboratory 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 reexamination 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 because of not-infrequent problems such as intolerance to MMF or severe infections in the early months after transplant when these data may be applicable.

Conclusion

The TICTAC trial is the first prospective test of single-drug 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 after transplantation.

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Disclosures

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References


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**CLINICAL PERSPECTIVE**

Cardiac transplantation has become the definitive treatment for eligible patients with end-stage cardiovascular disease, with durable 10- and 20-year outcomes. However, the immunosuppressive regimen that facilitates long-term positive outcomes is also responsible for chronic ill effects, including hypertension, weight gain, and malignancies. In the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial, the authors report on the first prospective, randomized effort to compare conventional dual-drug immunosuppression with single-drug therapy. In both study groups, corticosteroids were discontinued within the first 2 months, which was well tolerated. The authors report excellent outcomes, with a median of 3 years (range, 1 to 5 years) of follow-up, although the trial was limited to 150 patients at 2 centers. The importance of this trial is that it shows that immunosuppression can be reduced in a prospective fashion, allowing some patients to take only a single antirejection medication. In addition, the fact that corticosteroids were safely discontinued in all trial participants suggests that potentially this class of medication may be a less necessary part of the long-term treatment of these patients.
A Prospective, Randomized Trial of Single-Drug Versus Dual-Drug Immunosuppression in Heart Transplantation: The Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) Trial


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