ABSTRACT

This article reviews evidence related to the use of induction therapy and longer-term combination immunosuppressive drug regimens in cardiac transplantation. The introduction of new agents over the past 15 years has led to fewer rejection episodes and improved survival, and the focus has now shifted to prevention of long-term complications. Induction therapy with an interleukin-2 receptor antagonist, such as daclizumab, has become more common and use of muromonab-CD3 has diminished. However, the dangers of overimmunosuppression and side effects in the perioperative period are clear and induction therapy is currently reserved for patients at high risk of rejection and those with renal problems. In terms of chronic immunosuppressive therapy, tacrolimus leads to similar rejection rates and less hypertension and hyperlipidemia than cyclosporine; however, the newer calcineurin inhibitor may produce more diabetes. Mycophenolate mofetil (MMF) produces less rejection and improved survival versus azathioprine. Everolimus is also superior to azathioprine in terms of rejection and vasculopathy but leads to higher rates of bacterial infection and renal insufficiency. MMF and sirolimus produce similar rates of rejection over the long term. Sirolimus is associated with fewer viral infections, but is also stopped more often, usually due to renal issues, and also produces more fungal infections and impaired wound healing. Chronic immunosuppression must be tailored to the patient based on his or her individual issues. (Adv Stud Med. 2008;8(6):182-188)

CLINICAL DECISIONS REGARDING IMMUNOSUPPRESSIVE THERAPY IN HEART TRANSPLANTATION

Clinical decisions regarding immunosuppressive therapy in heart transplantation typically revolve around 3 key areas: (1) whether or not to use induction therapy; (2) how to construct a rational combination regimen for chronic immunosuppression; and (3) how to tailor immunosuppression for an individual patient based on risk factors, unique clinical characteristics, side effects, and other individual specificities. This article will cover these topics in the context of evolving immunosuppressive usage patterns and new evidence from randomized clinical trials.

INDUCTION THERAPY

The intensified period of specialized perioperative immunosuppression known as induction therapy is aimed at reducing rejection in the early postoperative period and also at reducing the risk of renal dysfunction related to use of calcineurin inhibitors. According to registry data from the International Society of Heart and Lung Transplantation (ISHLT), approximately 50% of heart transplant centers worldwide now employ some type of induction therapy in certain patients (Figure 1). Similar data for the United States, as reported by the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients, show that use of induction therapy increased from 31% of patients in 1996 to 52% in 2005. These registries also show that the type of induction therapy selected has changed over time, with steady or slightly declining use of polyclonal rabbit antilymphocyte globulin or antithymocyte globulin and sharp reductions in use of murine monoclonal CD3 antibody. The decline in muromonab-CD3 usage reflects the availability of the interleukin-2 (IL-2) receptor antagonists, basiliximab and daclizumab, which are better tolerated and, as discussed next, also quite effective in preventing rejection.

The largest randomized, double-blind, controlled
PROCEEDINGS

Figure I. Induction Therapies Used in Adult Heart Transplantation: Worldwide Data from ISHLT Registry

![Induction Therapies Used in Adult Heart Transplantation](image)

ALG = antilymphocyte globulin; ATG = antithymocyte globulin; IL-2R = interleukin-2 receptor; ISHLT = International Society of Heart and Lung Transplantation.


trial of daclizumab in induction therapy compared the efficacy of this IL-2 receptor antagonist against placebo in 434 cardiac transplant patients who were also on concomitant background therapy of cyclosporine, mycophenolate mofetil (MMF), and prednisone. The composite primary end point consisted of ISHLT grade 3A or greater rejection, hemodynamic compromise, death, or second transplant. Although there was a significant decrease in the primary end point in the daclizumab group at 6 months ($P = .007$), at 12 months there was only a nonsignificant trend toward a decrease in the composite end point: seen in 116 of 218 (53.2%) patients in the placebo group versus 97 of 216 (44.9%) in the daclizumab group ($P = .06$). Most of this treatment-related difference after 1 year was driven by a decrease in first biopsy-proven rejection: 101 of 218 patients on placebo (46.3%) versus 73 of 216 patients on daclizumab (33.8%).

Despite the benefit of daclizumab in terms of preventing rejection, there were trends toward increases in hemodynamic compromise (2.8% vs 1.4%) and mortality (7.4% vs 3.7%) in the active treatment arm at 12 months. These surprising results can be attributed to a flaw in the study design. When faced with early postoperative complications and the desire to withhold calcineurin antagonist therapy to preserve renal function, clinicians will often give an induction agent to prevent early rejection. Because clinicians in the study were blinded to the subject’s therapy, many subjects in the active treatment group were double-dosed with a second induction agent and, therefore, were possibly at increased risk for infection. Indeed, 8 of the 21 (38.1%) deaths in the daclizumab group occurred in patients receiving a second induction therapy versus 2 of 11 (18.2%) deaths in the placebo group. Six of the 8 patients (75%) who died after receiving double induction therapy died of infection. This study highlights not only the potential benefits of induction therapy in reducing rejection risk but also the danger of overimmunosuppression in the early postoperative period.

Results such as those just described plus the introduction of more potent alternatives for maintenance immunosuppression have led to continued caution in the use of induction therapy. In general, induction therapy should be reserved for patients considered at high risk for rejection, such as those who are presensitized because of prior exposure to foreign antigens and also young female patients. Patients at high risk of renal problems may also benefit. In these patients, the induction regimen allows sparing of a calcineurin inhibitor for 3 or 4 days until the creatinine recovers in the early postoperative phase.

THE EVOLUTION OF TRIPLE-DRUG THERAPY: BRIEF HISTORY OF MAINTENANCE IMMUNOSUPPRESSION

Agents used in maintenance immunosuppression have also evolved over the years based on the introduction of new agents and on the gradual accumulation of evidence from randomized trials. Clinicians will benefit from understanding the timeline of this evolution from the early 1990s when practically every heart transplant recipient was started on cyclosporine, azathioprine, and prednisone—the classic “triple therapy”—to today’s more diversified and individualized chronic regimens.

In the late 1990s, 2 key trials comparing tacrolimus with cyclosporine were published. Both the European ($N = 82$) and the American ($N = 85$) trial provided patients with a background of azathioprine and prednisone in addition to one of the calcineurin inhibitors; the studies also used a similar primary end point of freedom from grade 3A or greater rejection. In both trials, survival and rates of rejection were similar in the tacrolimus and cyclosporine groups over a full year.
Rates of nephrotoxicity were also similar in these year-long analyses. However, tacrolimus was associated with reduced frequencies of hypertension, hyperlipidemia, gingival hyperplasia, and hirsutism.

Also in the late 1990s, MMF was introduced as a possible alternative to azathioprine as an antiproliferative agent. In a large double-blind trial, cardiac transplant patients ($N = 650$) on a background of cyclosporine and corticosteroids were randomized to either MMF or azathioprine. In treated patients at 12 months, mortality was significantly reduced in patients taking MMF ($18/289, 6.2\%$ vs $33/289, 11.4\%$ in the azathioprine group, $P = .031$; Figure 2). There was also a significant reduction in rejection rates in those taking MMF as indicated by the reduced requirement for rejection treatment ($65.7\%$ vs $73.7\%$, $P = .026$).

Everolimus, a proliferation signal inhibitor (PSI), was first tested in the early to mid 2000s in a large randomized comparative trial against azathioprine. Two different doses of this agent, which inhibits IL-2 and IL-15 mediated T- and B-cell proliferation, or the comparator were given to heart transplant recipients ($N = 634$) in combination with cyclosporine, corticosteroids, and statins. The primary end point was a composite that included death, graft loss or retransplantation, biopsy-proven rejection of grade $3A$, or rejection with hemodynamic compromise. At 6 months, the percentage of patients reaching the primary end point was significantly smaller in the everolimus treatment groups ($27\%$ in the $3 \text{ g/kg/day}$ group, $P < .001$; $36.4\%$ in the $1.5 \text{ g/kg/day}$ group, $P = .03$) versus the azathioprine group ($46.7\%$). Also of extreme interest in this trial were results from intravascular ultrasonography showing that the average 12-month increase in intimal thickness was significantly reduced in the everolimus groups. In addition to a lower incidence of vasculopathy, which is explored in depth in another paper in this monograph, patients receiving everolimus also had significantly lower rates of cytomegalovirus (CMV) infection. However, azathioprine use was associated with less bacterial infection and less renal insufficiency.

Based mainly on the major studies just summarized, several shifts in the clinical use of immunosuppressive agents have occurred (Figure 3). Most notably, there has been a marked reduction in cyclosporine use—from $80\%$ in 2000 to $40\%$ in 2006—with a concomitant increase in tacrolimus use. Over this same period, the shift toward MMF and away from azathioprine is also apparent, as is a slight increase in sirolimus use.

In a first step toward establishing the most advantageous combination of newer immunosuppressive agents, $343$ cardiac transplant recipients were randomized $1:1:1$ to receive corticosteroids and tacrolimus + sirolimus, tacrolimus + MMF, or cyclosporine + MMF. After 12 months in this open-label trial, significantly fewer patients in the tacrolimus/MMF arm achieved the primary end point ($23A$ rejection or hemodynamic compromise) versus the cyclosporine/MMF group ($23.4\%$ vs $36.8\%$, $P = .029$). Differences in the incidence of any treated rejection were also sig-

![Figure 2. AZA (n = 289) Versus MMF (n = 289) in Heart Transplantation](image)
significant in favor of both tacrolimus arms: tacrolimus + sirolimus = 35%; tacrolimus + MMF = 42%; and cyclosporine + MMF = 59%; P < .001 (Figure 4). In terms of secondary end points and adverse events, the tacrolimus + sirolimus group had increased median levels of serum creatinine and renal dysfunction (Table), increased triglycerides, and no differences in total or high-density cholesterol. It is unclear whether the renal issues in this group were because of the combination or sirolimus itself. The tacrolimus + sirolimus group also encountered fewer viral infections but more fungal infections and impaired wound healing. There was also a trend toward increased diabetogenic effects in the tacrolimus arms on balance, and especially given the antirejection efficacy and lower rates of discontinuation and renal dysfunction seen with the tacrolimus + MMF combination, the authors concluded that tacrolimus + MMF may be the best choice for many patients.

**TAILORING THERAPY**

No single regimen is going to achieve the ideal balance of antirejection efficacy and long-term safety for every patient. When tailoring immunosuppressive therapy, many clinicians think first of limiting corticosteroids in order to reduce side effects. The adverse effects of the corticosteroids are indeed widely acknowledged and one small nonrandomized trial has documented that carefully weaning transplant patients (N = 41) off steroids significantly reduces infections (0.64 infections/patient/year vs 0 [P = .001]) at 6 months posttransplant. However, this same study showed no significant improvements in blood pressure, body mass index, blood sugar, total cholesterol, or low-density lipoprotein cholesterol at the half-year mark.

Although the longer-term benefits of steroid weaning may be more obvious, this has yet to be documented, and clinicians need to start evaluating the other drugs and dosages in the combination regimen to find the appropriate levers for adjusting and improving therapy. As indicated in the ISHLT registry, there is ample room for therapy improvement given the current rates of hypertension (74.4%), renal dysfunction (30.4%), hyperlipidemia (67.8%), and diabetes (31.5%) found in heart transplant patients 1 year after their operation (2002–2006 data).
Based on the evidence reviewed in this article, one example of how therapy can be adjusted to limit side effects involves the patient with renal insufficiency at baseline. This is a patient who should probably not receive a combination of tacrolimus + sirolimus. Similarly, a pretransplant patient with a left ventricular assist device and a driveline infection (ie, a patient likely due for a long complicated postoperative course and at a higher risk for infection) would likely not be suitable for sirolimus because of the drug’s association with poor wound healing and bacterial and fungal infections. On the other hand, a patient who is CMV negative with a positive donor organ may be a very appropriate candidate for the tacrolimus + sirolimus combination because of its association with reduced viral infections. Key factors to weigh in treatment decisions, including cardiac vasculopathy, nephrotoxicity, infection, and malignancy, are discussed in the following 2 articles of this monograph.

**Table. Adverse Events in Comparison of 3 Combination Immunosuppression Regimens in Cardiac Transplantation**

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Tacrolimus/Sirolimus (n = 111)</th>
<th>Tacrolimus/MMF (n = 108)</th>
<th>Cyclosporine/MMF (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of tacrolimus or cyclosporine</td>
<td>24 (21.6)</td>
<td>9 (8.3)</td>
<td>25 (21.7)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>9 (8.1)</td>
<td>1 (0.9)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>Refractory rejection</td>
<td>0</td>
<td>0</td>
<td>13 (11.3)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>2 (1.8)</td>
<td>4 (3.7)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Discontinuation of MMF or sirolimus</td>
<td>39 (35.1)</td>
<td>18 (16.7)</td>
<td>17 (14.8)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (4.5)</td>
<td>8 (7.4)</td>
<td>7 (6.1)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>9 (8.1)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (4.5)</td>
<td>5 (4.6)</td>
<td>0</td>
</tr>
<tr>
<td>Infection n = 109</td>
<td>9 (8.3)</td>
<td>22 (20.4)</td>
<td>23 (20.2)</td>
</tr>
<tr>
<td>Viral CMV infection/syndrome</td>
<td>3 (2.8)</td>
<td>14 (13)</td>
<td>14 (12.3)</td>
</tr>
<tr>
<td>Fungal</td>
<td>18 (16.5)</td>
<td>8 (7.4)</td>
<td>13 (11.4)</td>
</tr>
<tr>
<td>Candida</td>
<td>14 (12.8)</td>
<td>7 (6.5)</td>
<td>12 (10.5)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>39 (35.8)</td>
<td>37 (34.3)</td>
<td>42 (36.8)</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; MMF = mycophenolate mofetil.
Adapted with permission from Kobashigawa et al. Am J Transplant. 2006;6:1377-1386.11

**CONCLUSIONS**

The increasing number of immunosuppressive agents has contributed to reduced rates of rejection and improved survival after cardiac transplantation. As these key outcomes have improved, the goal has expanded to include prevention of the long-term complications of drug therapy. Although data from multicenter clinical trials are absolutely necessary to guide decision making in combination immunosuppression, these data always need to be interpreted and applied to tailored therapy for individual patients.

**DISCUSSION**

*Ms Carter:* Our biggest issue in the clinic is the side effects of these medications. We see many difficulties when we are switching regimens, for example, if we are trying to counteract graft vasculopathy by using sirolimus. Patients complain frequently with that particular drug. But it is often difficult to figure out exactly which medicine is causing the side effects.

*Dr Rogers:* Yes, we spend a lot of time managing side effects. In trying to minimize renal dysfunction while maintaining potency, for example, we manipulate drug doses and experiment with different regimens.

*Dr Eisen:* The side effects may also affect patient adherence and, ultimately, outcomes. Again, that is why we need a better way to control the immune system and reach a happy medium between over- and underimmunosuppression. Weaning patients off steroids, which has become the norm, has gone a long way to minimizing side effects. But there is more to do in terms of reducing cyclosporine doses or perhaps eliminating other agents.

*Dr Conte:* Dr Russell showed how medication use has evolved over time. What about the patient who is 10, 15, 20 years out? If a patient is doing well on an older regimen, do we leave well enough alone?

*Dr Kobashigawa:* I do abide by “if it ain’t broke why fix it?” We have many patients who have been on azathioprine and cyclosporine for 15 or 20 years who have been doing very well. Now, many patients are off
corticosteroids by the end of the first year. We customize immunosuppression, for example, in older patients to account for immunosenescence. In these older patients, we often come down on the calcineurin inhibitor levels and wean off corticosteroids without problems. On the other hand, we watch those at risk for rejection much more carefully, such as multiparous females. I agree with the previous comment about sirolimus side effects. Close to 50% of our patients need to be taken off sirolimus after initiation. In our comparison of sirolimus to everolimus, which is not yet approved in the United States, many patients appeared to tolerate everolimus better.

**Dr Eisen:** Our appreciation of certain risk factors has changed. Until fairly recently, for example, many of us were willing to tolerate modestly elevated creatinines long-term if the patient was doing well. But with recent data showing that creatinines as low as 2.0 impart significant risk, we are more likely to modify the immunosuppression, perhaps reducing the cyclosporine a bit further, to improve their outcome.

**Dr Kobashigawa:** Creatinine is certainly one factor everybody evaluates but we should not fixate only on that. When you look at the registry data, the major factor limiting long-term survival is not renal dysfunction or even cardiac allograft vasculopathy but malignancy. Now, all immunosuppressive agents may unavoidably contribute to cancer but the PSIs may have simultaneous antitumor properties. Renal transplant data suggest that these agents may actually decrease the amount of Kaposi’s sarcoma. And renal transplant registry data suggest less solid organ tumors in patients on PSIs. But what does this mean for heart transplant patients who develop cancer? Should they be switched to a PSI?

**Dr Eisen:** Given that data, and despite the lack of controlled studies in heart transplantation, I would certainly consider adding a proliferation signal antagonist. Also consider that various congeners of these agents are already being used as adjunctive therapy for renal cell carcinoma. However, we still have problems if the doses used are much higher than normal. Prevention of cancer would of course be preferable and, again, what we need is a better tool for gauging the appropriate amount of immunosuppression without putting our patients at risk.

**Dr Rogers:** Our general approach to malignancy has been to minimize the immunosuppression, but we have lacked the data to guide us. At the same time, we all work hard to keep other providers from stopping immunosuppression entirely, because ultimately, we know those patients invariably reject and end up getting more immunosuppression. Regarding the PSIs, perhaps what is needed is a randomized study across all organs comparing lowered doses of a standard regimen versus switching over to the PSIs.

**Dr Russell:** We recently had an oncologist ask for permission to start one of our patients on sirolimus because it was part of the usual regimen for that malignancy. But in general, I agree, our starting approach is to get the immunosuppression as low as possible, but not so low as to cause rejection.

**Dr Conte:** What do we do with patients who need transplantation but who have had malignancies, such as breast cancer or colon cancer? Do we wait?

**Dr Rogers:** It is complicated because the cancer literature on recurrence risk does not include immuno-suppressed patients. We probably underestimate the risk of recurrence. We see many patients with prostate malignancies and our general approach here has been to individualize therapy based on malignancy grade and the related predicted risk of occurrence. We then try to determine the appropriate amount of time to wait while the patient is disease-free before we proceed with transplantation.

**Dr Kobashigawa:** Conventionally, we have waited for a 5-year malignancy-free period before transplantation. But this convention was not really based on any evidence. The recent consensus conference from the ISHLT recommends that the decision be individualized. As Dr Rogers suggests, a patient with a well-differentiated prostate cancer can last more than 10 years with a very good prognosis. Every case should be evaluated by an oncologist for prognosis based on type and grade of cancer.

**Dr Eisen:** The other unresolved question involves cancer screening after transplantation. The standard American Cancer Society approach is based on non-immunosuppressed patients, so how effective is that? Do we do colonoscopies every 5 years according to the standard recommendation? How do we screen women who have had breast cancer? All this is open to interpretation in our transplant population.

**REFERENCES**


