Therapeutic Immunosuppression in Cardiac Transplantation

JOHN A. ROBINSON, M.D. and JOHN B. O'CONNELL, M.D.

Loyola University Medical Center, Maywood, IL 60153

ABSTRACT

There is continual re-evaluation of immunosuppressive protocols as clinical experience increases in cardiac allotransplantation. Loyola University Medical Center has performed 44 heart transplants over a span of 18 months. The initial protocol was a distillate of several established regimens (Stanford, Pittsburgh, and Papworth). Since its inception, cyclosporine loading dosage has been reduced between 20 to 50 percent. Azathioprine in graded dosage is automatically added immediately post transplantation, corticosteroids are rapidly decreased, and cumulative antithymocyte globulin dosage is less. Except for the use of methotrexate as a last alternative, rejection episodes are treated conventionally. Very little nephrotoxicity has occurred with any of the protocols.

Introduction

The introduction of cyclosporine (CY) as an immunosuppressive and immunomodulating agent was a signal advance in cardiac allotransplantation. This fungal, hydrophobic undecapeptide provides both highly focused suppression of allograft cytotoxicity and reductions in corticosteroids requirements to levels previously impossible to reach. The latter benefit was immediately translated into a reduction in serious, uncontrollable infections in the immediate post-transplant period. This, in combination with decreased serious allograft rejection episodes, was immediately reflected in increased actuarial survival in the first six month post-transplant period. The morbidity of CY, initially thought to be significant in terms of nephrotoxicity, has proven to be minimal, at least in the setting of cardiac allotransplantation, as clinicians realize that lower loading and maintenance doses provide adequate suppression of rejection.

Materials and Methods

The 44 patients who have undergone orthotopic cardiac allotransplantation had either ischemic or idiopathic dilated cardiomyopathy. By definition, they were not considered suitable candidates for valve replacement or aorto-coronary bypass.

Results

Loyola University Medical Center (LUMC) began its cardiac transplantation program on March 11, 1983. To
date, 44 orthotopic cardiac transplants have been done, and, as clinical experience increases, beneficial modifications of the original immunosuppressive protocol have been made (table I). In addition, the unexpected relative unavailability of one of the major immunosuppressive medications also forced several unexpected modifications. Initially, the LUMC immunosuppressive regimen was: CY 10 mg per kg p.o. from four to six hours prior to transplant accompanied by 500 mg of methylprednisolone (MP) intravenously (IV); and equine antithymocyte globulin (HATG), 5 mg per kg IV, over a period of four to six hours. Cytomegalovirus (CMV) negative blood products were and are used in all CMV-negative recipients. Upon successful circulatory support by the donor heart, another 500 mg of MP is given IV. During the next 24 hours, 125 mg MP was given every eight hours and then oral prednisone was begun at one mg per kg and reduced by 0.2 mg per kg decrements every two days to a maintenance dose of 0.3 mg per kg. Equine antithymocyte globulin was continued at five mg per kg daily for 10 days and then discontinued. Initially, dosage of HATG was monitored and adjusted daily by attempting to maintain daily absolute T-cell counts at approximately 200 per mm$^3$. It was found to be highly unpredictable in many patients and, more importantly, did not have any direct relationship between T-cell lymphopenia and rejection episodes. Ultimately, this variable was judged not useful as a predictor of rejection or therapeutic efficacy and it was abandoned.

Cyclosporine dosages were given orally in a twice daily dose that was determined by the previous 24 hr interval trough level. Initial attempts were made to maintain a CY trough level of approximately 200 ng per ml or less (determined on serum at room temperature by standard radioimmunoassay). It was soon apparent that, unless there were interacting drugs being used in concert with it, a loading dose of 10 mg per kg CY frequently required downward adjustment to approximately five mg per kg within 72 to 96 hours in most recipients to avert toxic trough levels. This clinical observation, coupled with the increasing recognition by many others that initial loading doses could be reduced without clinical evidence of loss of immunosuppression, prompted a reduction of loading dose to five mg per kg to maintain trough levels in the area of 100 to 150 ng per $\mu$l (table II). Although this caused a slightly longer period to achieve therapeutic trough levels, adequate immunosuppression was still operative since patients were also on HATG.

However, the national shortage of HATG, perhaps a fortuitous external event, forced a revision of the protocol again that included slightly higher cyclosporine loading dosages (8.0 mg per kg) in order that an earlier immunosuppressive trough level might be achieved. The intervals between corticosteroid decrements were lengthened to provide fur-
TABLE II

Modifications of Original Immunosuppressive Protocol

Reduction of cyclosporine loading dose to 5.0 mg per kg per day

In response to antithymocyte globulin shortage:
Redocket of cyclosporine loading dose to 8.0 mg per kg
Addition of azathioprine in immediate postoperative period in graded doses of 0.5 to 2.0 mg per kg

Other suppression as the HATG was shortened to seven days. Lastly, low dose azathioprine (AZP) was begun at day one to two post-transplantation for reasons that are discussed in the following paragraphs.

Rejection episodes are initially treated in somewhat conventional fashion (table III). The initial episode is treated with daily pulse MP, 500 mg, for three days. Subsequent episodes of rejection are treated with pulse MP therapy plus five days of HATG at a dose of five mg per kg. Any rejection episode associated with significant hemodynamic changes, i.e., significant cardiac index/filling pressure changes, (by right heart catheterization at the time of biopsy) is treated with both MP and HATG. Many mild episodes of rejection can be handled simply with short term increases in oral corticosteroids. Persistent or nonreversible episodes of rejection, when present, required the addition of azathioprine. Azathioprine was added in this manner only to patients transplanted early in the program who had not been automatically placed on AZP in the immediate postoperative period. Initially, AZP was a mainstay for prevention of allograft rejection, but it lost some of its popularity when cyclosporine was introduced. However, AZP is now undergoing a resurgence in usage based mainly on the increasing clinical impression that, while initial fulminant rejection episodes are less with CY therapy, persistent or smoldering long term chronic rejection remains a most nettlesome and significant problem in cardiac allograft transplantation. When all the previous therapy combinations failed in five patients, methotrexate was added in 25 to 50 mg IV bolus dosages weekly and has been successful in reversing persistent cell infiltration. There have been several significant episodes of leukopenia with this methotrexate low dose regimen, perhaps, secondary to decreased renal excretion caused by cyclosporine or an additive bone marrow effect with azathioprine. One patient in the early posttransplant period failed on all rejection regimens (methotrexate not given) and responded to seven days of monoclonal anti-T-lymphocyte (OKT-3) therapy (Ortho Monoclonal protocol).

The easiest way to avert cyclosporine toxicity, especially renal, is to identify pretransplant cues that are associated with it (table IV). If a patient in the pretransplant period has significant renal dysfunction or has been on an aminoglycoside antibiotic and/or has significant hepatic congestion, the loading CY dose is reduced to 2.0 mg per kg. When cyclosporine proves to be significantly nephrotoxic and creatinines are greater than 3.0 mg per ml and do not improve after reduction of CY dosage, the drug is discontinued over a period of 30 days while slowly introducing, if the patient is not already on it, AZP at low dosage (0.5 mg per kg). Azathioprine is slowly increased to a maximum of 2.0 mg per kg

TABLE III

Treatment of Rejection

Initial: Pulse methylprednisolone (MP) = 500 mg
Subsequent: Pulse MP plus antithymocyte globulin (5 mg per kg x 5 days)
Any rejection episode associated with unexplained hemodynamic deterioration: Pulse MP and equine antithymocyte globulin

"Persistent" or nonreversible rejection:
weekly IV methotrexate
TABLE IV

Modifications of Cyclosporine Dosage
with Predicted or Actual Toxicity

Loading dose reduced to 2.0 mg per kg if
pretransplant renal/hepatic dysfunction present
Anticipate decreased dosage if patient received
aminoglycoside antibiotics
Discontinued over 30 days as azathioprine
introduced if serum creatinine > 3.0 and does
not decrease on lower dosage

over a period of 30 days. If the patient is
already on maximal doses of AZP, the CY is discontinued over a two week
period. Discontinuance of CY has been
relatively rare in our group of patients,
occuring only twice in 44 transplants.

Seizures, especially in the very early
post-transplant period, have occurred in
four patients. These seizures required
dilantin for control. The use of this anti­
convulsant predictably increases CY
requirements by a factor of three to five
times the patient’s usual maintenance
dose.

At present, our institution has an 84
percent actuarial survival rate (seven
deaths per 44 transplants). There has
been an average of 1.2 rejection episodes
per patient. Four deaths were due to
acute rejection, one owing to chronic
rejection, and two perioperative deaths
were associated with either high pulmo­
nary vascular resistance or an ischemic
bowel syndrome. A potentially lethal
effect of chronic rejection is a vasculo­
pathy in the donor graft. This culminates
in a clinical syndrome of either painless
acute myocardial infarction or progres­sive pump failure. This occurred in one
patient who became a candidate for
emergency retransplantation. Unfortu­
nately, a suitable donor for retransplan­
tation could not be obtained in time.

Significant infectious disease complica­tions have been few, the majority
being self-limited oral herpes simplex.
There was one incident of toxoplasma
retinitis and myocarditis. The latter
resolved without significant visual acuity
loss on sulfa-pyrimethamine therapy.
There was also a patient who developed
necardiosis involving an eye and epi­
dyamus and who is on chronic sulfa ther­
apy. There have been two episodes of
perioperative sepsis, an aspiration pneu­
monia, and an episode of gram negative
bacteremia. Both were successfully
treated with third generation cephalo­
sporins. There have been no significant
Epstein-Barr virus infections or lymphomas. Six CMV positive donor hearts
have been used of which four were
transplanted into CMV negative recipi­
ents. All four patients seroconverted
without serious clinical manifestations or
correlation with rejection within three
months of transplantation.

Discussion

Several points of interest emerge from our
experience with continual readjust­
ment of therapy protocols. First and
foremost, the experience-driven protocol
changes underscore the point that, at
present, there is no scientific or clinical
consensus on a “standard” immuno­suppressive regimen in cardiac allotrans­
plantation. Second, the initial protocols
used very high cyclosporine dosages. It
has become evident that much lower
dose schedules provide adequate rejec­tion control and marked reduction in
nephrotoxicity. The loading dose used by
us is less than 50 percent of the original
recommendations. Lastly, the transient
HATG shortage forced the issue of eval­
uation of monoclonal anti-T3 therapy for
both immediate postoperative and sub­
sequent rejection episodes.

What does the future hold? Currently,
we are considering a randomized proto­
col using monoclonal T-cell antibodies in
one arm in lieu of HATG and are also
considering the use of pretransplant
cyclosporine to enhance graft tolerance.
by simulating the effect of donor specific transfusions.\(^1\)

Cyclosporine, although a significant advance, is not the unblemished panacea of cardiac transplantation. Further work is urgently needed in separating the immunologically active portions of the molecule from the nephrotoxic moieties. The full spectrum of immunologic actions of cyclosporine are not fully understood. Two effects are well described: CY has no effect on specific alloantigen recognition, but it inhibits subsequent expansion of allo-specific cytotoxic T lymphocytes by inhibiting their ability to produce the critical growth factor II-2.\(^5\) However, the main effect of cyclosporine on suppression of rejection episodes may ultimately prove to be entirely different. In many ways, CY reproduces both the neonatal state of tolerance and radiation induced state of antigen specific tolerance.\(^6\) In both these latter states, a population of alloantigen specific suppressor cells arise if a graft is introduced with appropriate timing. It is, therefore, understandable that there is increasing interest in CY’s ability to enhance expansion of both nonspecific and, more importantly, a similar group of antigen specific T suppressor cells. The presence of antigen specific suppression of allograft rejection, at least in some situations, persists even after discontinuation of cyclosporine; in other circumstances, it will persist only if both the allograft remains in place and cyclosporine is continued.\(^3\) Pharmacologic manipulation of this drug properly may be the most significant advance in clinical transplantation yet.

References