

2/23/2005 1:52 PM

Everolimus in Heart Transplantation

Position Paper

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Table of Contents

1	Introduction/Executive Summary.....	3
2	Chronic allograft vasculopathy: unmet medical need in cardiac transplantation.....	3
2.1	Etiology of CAV.....	4
2.2	The study of the early natural history of allograft vasculopathy has been revolutionized by the use of intravascular ultrasound	4
2.3	Coronary artery intimal thickening measured by IVUS strongly correlates with long-term clinical outcomes	5
3	The beneficial effect of everolimus on CAV	6
4	Other efficacy benefits of everolimus include a reduction in acute rejection and CMV infection.....	8
4.1	Acute rejection.....	8
4.2	Cytomegalovirus	9
5	Management of everolimus safety.....	10
5.1	Exposure-effect relationships for everolimus and CsA in heart transplantation... ..	10
6	Labeling guidance on everolimus in heart transplant now is preferred to leaving clinicians to unguided use sirolimus out-of-label.....	12
7	Summary.....	13
8	References	14

1 Introduction/Executive Summary

This position paper represents a summary of the therapeutic needs and an important new potential treatment option in cardiac transplantation. As part of an adequate and well-controlled safety and efficacy trial for registration of everolimus (B253), a prospectively planned study of allograft vasculopathy was performed using state of the art methodology and longitudinal evaluation. The everolimus B253 study provides the most robust evidence to date that an orally administered mTOR inhibitor can significantly blunt the progression of cardiac allograft vasculopathy, the greatest unmet need in cardiac transplantation. This is not a surprise, as these results are consistent with a host of experimental evidence. Both everolimus and the related agent sirolimus are active in preclinical atherosclerotic, mechanical and alloimmune vascular injury models as well as in the clinical setting. We recognize methodological concerns about how the intravascular ultrasound (IVUS) data were obtained in the everolimus study. Nevertheless, the evidence, as will be discussed, suggests that the treatment effect on allograft vasculopathy is real, and evaluable in the context of the population of cardiac transplant patients receiving everolimus for at least 1 year.

We recognize the importance of everolimus in transplantation medicine, and also the need to gain Food and Drug Administration (FDA) approval in cardiac transplantation in order to ensure its availability to our patients. It is our opinion that:

- The potential for benefit overall outweighs the potential safety issues, particularly if the clinicians are fully apprised of the potential for interaction with CsA to raise creatinine.
- The dataset is therefore adequate to support the indication of heart transplantation now.
- Labeling guidance on everolimus in heart transplant now is preferred to leaving clinicians unguided in the use of sirolimus out-of-label.
- A risk minimization program should be in place until such time that a regimen with optimized renal safety is prospectively defined.
- Waiting to repeat new studies in order to explore the impact of reduced CsA exposure on renal function will deprive patients of a promising treatment to prevent rejection and vasculopathy.

2 Chronic allograft vasculopathy: unmet medical need in cardiac transplantation

Cardiac transplantation has become the established treatment of choice for eligible patients with end-stage congestive heart failure and the transplant community needs the best therapies available to ensure organ recipient survival.

- There is a limited availability of donor organs.
- In cardiac transplantation graft loss equals death (unless a rare re-transplant is done).
- Survival outcomes in cardiac transplantation are inferior to those in kidney and liver transplantation (UNOS 2003).

Coronary artery disease in the transplanted heart, also known as chronic allograft vasculopathy (CAV), is the major cause of mortality late after transplantation (Taylor 2003). It affects up to 50% of all heart transplant recipients within 5 years of surgery (Kobashigawa 2000).

The diffuse nature of vessel involvement limits the potential for successful revascularization, hence the emphasis on agents to prevent progression of vascular remodeling. Unfortunately there is no established treatment for CAV. Re-transplantation is uncommonly performed due to the poor outcomes seen with re-transplantation as well as the limited organ supply.

2.1 Etiology of CAV

The mechanisms of CAV are multifactorial and include both immune and non-immune factors. (Pinney 2004, Caforio 2004, Valantine 2004, Kirklin et al 2003, Kobashigawa 2000, Grattan 1989).

- Ischemia of the graft at the time of transplantation is one of the more important non-immune factors, because this leads to endothelial cell injury.
- Immune factors involving cellular and humoral rejection can further insult the vascular endothelium, leading to a cascade of immunologic responses.
- There may be an association between acute rejection and CAV.
- CMV infection results in anti-endothelial antibodies, and is associated with CAV.
- Acute rejection with hemodynamic compromise and multiple rejections increase the risk of CAV.
- Host metabolic factors associated with increased risk for CAV are diabetes, and dyslipidemia.

2.2 The study of the early natural history of allograft vasculopathy has been revolutionized by the use of intravascular ultrasound

Intravascular ultrasound (IVUS) has emerged as the new gold standard for atherosclerosis imaging because it provides cross-sectional images of both the arterial wall and lumen with excellent resolution, reveals the diffuse nature of atherosclerosis and the involvement of reference segments, and takes into account vessel wall remodeling (Guedes 2004).

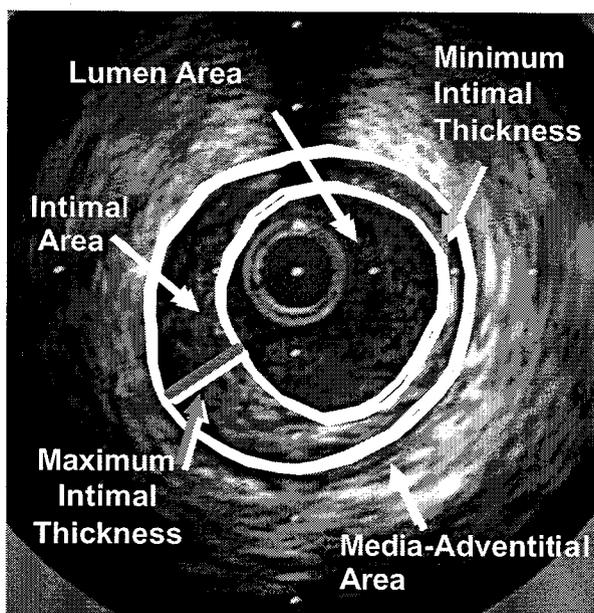
Thus, IVUS has become an important tool in the evaluation of CAV.

- IVUS is a sensitive approach for the detection of vasculopathy (Jimenez 2001, Kapadia 1998, Liang 1996).
- The method to perform and interpret IVUS has been standardized (Mintz 2001).
- IVUS can be used to assess coronary artery intimal proliferation serially over time (Mintz 2001, Kapadia 1998).

2.3 Coronary artery intimal thickening measured by IVUS strongly correlates with long-term clinical outcomes

Several early studies found an association between intimal thickness post-transplant and the subsequent development of angiographic transplant coronary artery disease and mortality (Rickenbacher 1995, Mehra 1995, Kapadia 1999). More recently, a change in maximal intimal thickness of > 0.5 mm from baseline to one year post-transplant has become established as the key measure of CAV (Kobashigawa 2003). A typical IVUS image is depicted in Figure 1.

Figure 1. A typical IVUS image with arrows depicting key measures of vasculopathy.



A recent study presented at the meeting of the International Society of Heart and Lung Transplantation (Kobashigawa 2004) showed that a change in intimal thickening of 0.5 mm in the first year after transplant appears to be a reliable marker for subsequent development of angiographic evidence of cardiac allograft vasculopathy and mortality up to 5 years after heart transplantation. This multi-center study utilized a blinded core lab to assess baseline and 1-year IVUS values in 125 patients in whom 5 year follow-up data could be obtained. An increase in maximal intimal thickness of > 0.5 mm during the first year post-transplant was associated with a 5-year mortality of 21 % compared to 6% for those without this degree of change in intimal thickness. The composite of major adverse cardiac events, graft loss or death was 46% in the > 0.5 mm group vs. 17% in those with less than a 0.5 mm change in maximal intimal thickness.

Overall, the rapid progression in first-year intimal thickening as detected by IVUS appears to represent the cumulative effects of adverse events that ultimately lead to poor clinical outcome (Kobashigawa 2003).

3 The beneficial effect of everolimus on CAV

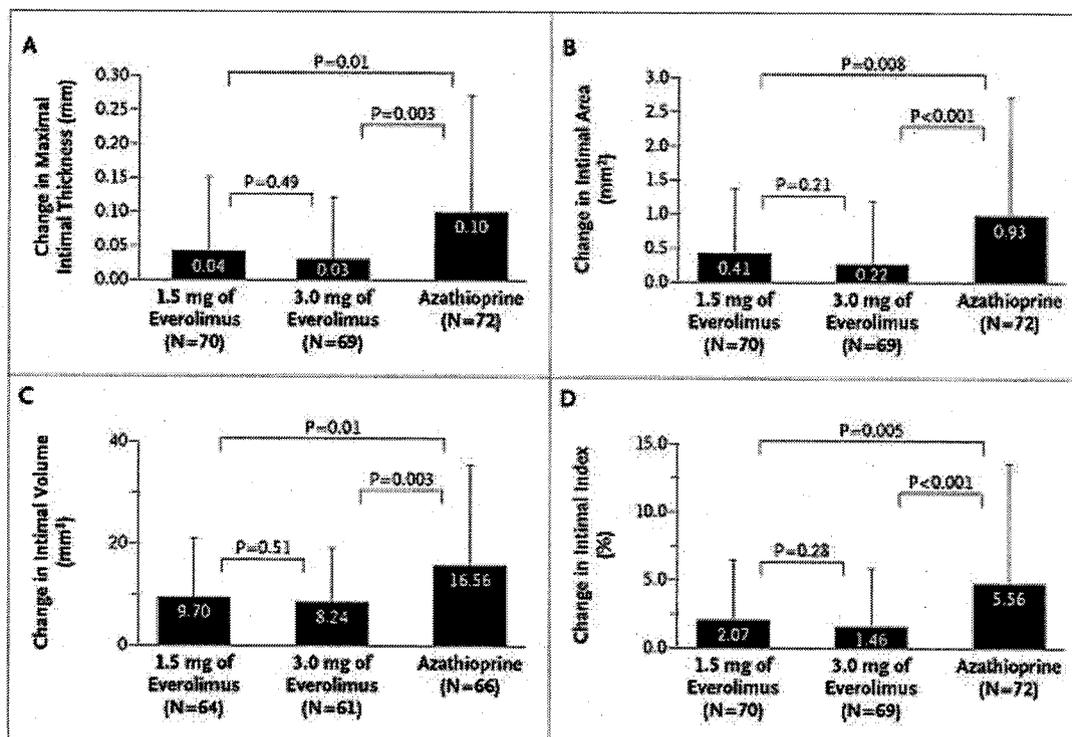
The benefit of everolimus in reducing the incidence and severity of CAV is an important advancement in the management of heart transplant recipients that hitherto has not been demonstrated as part of a large clinical trial experience. This finding is consistent with the mechanism of action of inhibiting vascular smooth muscle proliferation and is consistent with preclinical studies (Cole 1998).

In the published trial with everolimus, study B253 (Eisen 2003), a total of 634 patients were randomly assigned to receive 1.5 mg of everolimus per day, 3.0 mg of everolimus per day, or 1.0 to 3.0 mg of azathioprine per kilogram of body weight per day, in combination with cyclosporine, corticosteroids, and statins. Per protocol, IVUS examinations were to be performed both at baseline and 12 months in patients that were still on study medication. Ultimately, 70 of the 209 patients (33%) in the 1.5 mg everolimus arm, 69 of the 211 patients (33%) in the 3mg everolimus arm and 72 of the 214 patients (34%) in the AZA arm, had paired baseline and 1-year IVUS tapes that were technically adequate (including at least 11 site matched-slices) for interpretation. The 211 patients with technically adequate baseline and 1 year IVUS examinations met the prospectively defined sample size definition. Physicians performing IVUS and interpreters of IVUS were blinded as to treatment assignment. While not all patients were able to undergo both baseline and one year IVUS examinations, this is a very large cohort of patients and the patient numbers and demographic features are similar across treatment groups. Moreover, many patients who did not have matching IVUS studies were excluded for technical reasons not subject to bias. While there was the potential for bias based on renal function (patients with elevated creatinine levels less likely to undergo IVUS) or other treatment-emergent features, comparison of efficacy failure and creatinine clearance between those with paired IVUS results and those without suggested that there was no bias for higher creatinine clearance among everolimus-treated patients undergoing IVUS. It is interesting to note that similar numbers of patients in each group had IVUS performed, despite differences in renal function. Consistent with prior studies (Kobashigawa, Starling 2003), logistic regression analysis demonstrated creatinine clearance was not associated with the development of intimal thickening or CAV measured by IVUS (data on file at Novartis). Thus, we consider the B253 IVUS population to be typical of, and relevant to, the larger population of patients, who will potentially benefit from treatment with everolimus.

The key findings in the IVUS study were:

- At 12 months the incidence of vasculopathy (pre-defined as an increase of maximal intimal thickness of 0.5 mm from baseline) was significantly lower in the 1.5-mg group (35.7 percent, $P=0.045$) and the 3.0-mg group (30.4 percent, $P=0.01$) than in the azathioprine group (52.8 percent).
- Other IVUS analyses are depicted below in Figure 2:

Figure 2. Mean (\pm SD) Change in Maximal Intimal Thickness (Panel A), Intimal Area (Panel B), Intimal Volume (Panel C), and Intimal Index (Panel D) from Base Line to 12 Months.



These data are concordant in demonstrating the benefit of everolimus in reducing all measures of blood vessel remodeling. An important point supporting the robust nature of this finding is both its consistency across all pre-defined measures of vascular remodeling, as well as the size of the treatment effect.

Given the rigor of the IVUS protocol employed the demonstration of effects of everolimus on CAV should not be considered surprising. They are consistent with the mechanism of action and pre-clinical findings. In addition, a related compound, sirolimus, has been studied in both the de novo and maintenance studies with corroborative results.

- A study of sirolimus vs. AZA in de novo cardiac transplant recipients (Keogh 2003) suggested a similar vasculopathy benefit.
- Another study in patients with established vasculopathy showed that treatment with sirolimus slowed disease progression (Mancini 2003).

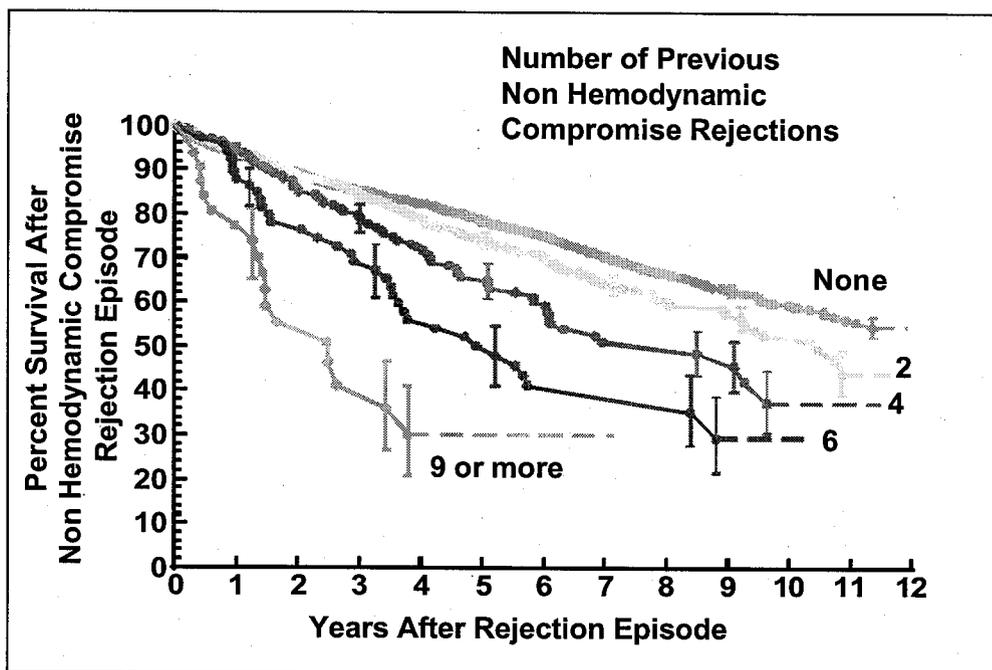
Finally, studies of both sirolimus (Sharma 2002, Moses 2003) and everolimus (Grube 2004) drug-eluting stents further support the ability of this class of drugs to inhibit pathological vascular remodeling.

4 Other efficacy benefits of everolimus include a reduction in acute rejection and CMV infection

4.1 Acute rejection

Uncomplicated acute rejection may engender little immediate risk to patients, yet its treatment is not without complications (infection, malignancy, steroid side effects), and longer-term complications of acute rejection may limit patient and graft survival. Analysis of the Cardiac Transplantation Research Database (CTRD) demonstrates the desirability of remaining rejection free. Figure 3 shows that the number of acute rejections is a risk for mortality.

Figure 3. CTRD data- effect of rejection on survival



data courtesy of Dr. James Kirklin, University of Alabama, presented at ISHLT 2004

Efficacy in the Everolimus B253 study:

In study B253 the primary efficacy endpoint (a composite of ISHLT grade=3A rejection, graft loss and death) was met at 12 months, and a clinically meaningful and statistically significant benefit could be demonstrated through 24 months (Table 1). The main driver of this result was an improvement acute rejection of ISHLT grade=3A (Figure 4).

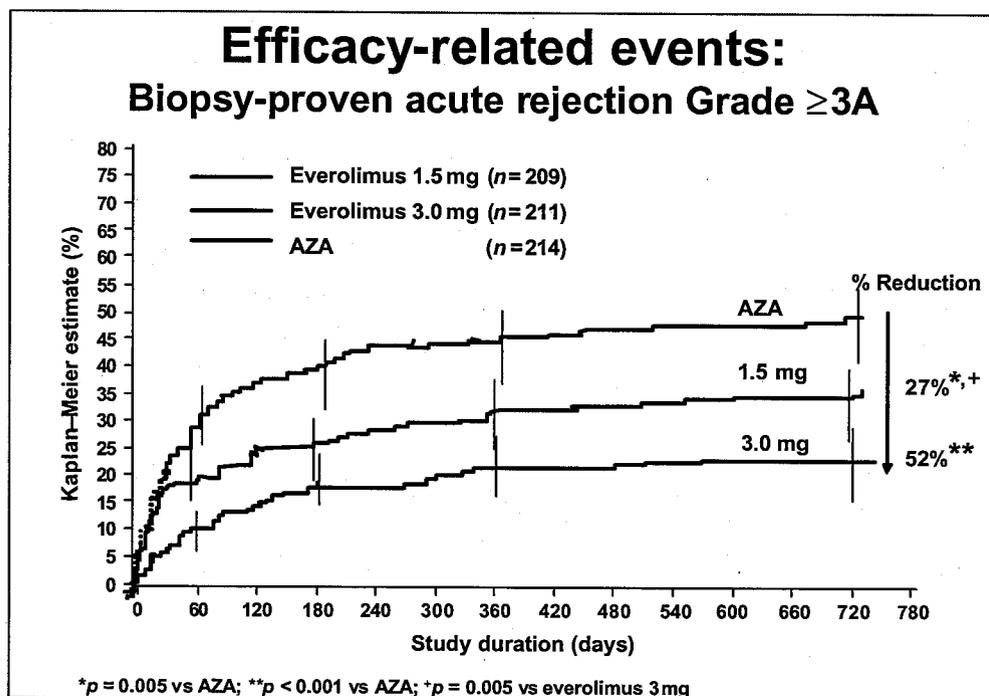
Table 1. Incidence of the Primary End Point. The primary end point was a composite of biopsy-proven acute rejection of at least grade 3A, acute rejection associated with hemodynamic compromise, death, graft loss, or loss to follow-up during the first year.

Month 6				
	Ever 1.5 mg (N=209)	Ever 3 mg (N=211)	AZA (N=214)	p-value
Acute rejection of ISHLT = grade 3A, acute rejection associated with HDC, graft loss, death or loss to follow-up	76 (36.4%)	57 (27.0%)	100 (46.7%)	0.031 ^a <0.001 ^b 0.037 ^c
Month 12				
	Ever 1.5 mg (N=209)	Ever 3 mg (N=211)	AZA (N=214)	p-value
Acute rejection of ISHLT = grade 3A, acute rejection associated with HDC, graft loss, death or loss to follow-up	87 (41.6%)	68 (32.2%)	113 (52.8%)	0.020 ^a <0.001 ^b 0.045 ^c

Source: Eisen 2003

a: Ever 1.5 mg vs. AZA; b: Ever 3 mg vs. AZA, c: Ever 1.5 mg vs. Ever 3 mg (pairwise Z-test, $p = 0.05$).

Figure 4. Acute rejection represents the majority of efficacy events and are markedly reduced by Everolimus



4.2 Cytomegalovirus

Considerable evidence suggests a role for viruses in CAV, including observational data, experimental models and therapeutic trials implicating human cytomegalovirus (CMV) in the progression to CAV (Weill 2001, Grattan 1998). The development of anti-endothelial

antibodies as a result of CMV infection is one of several mechanisms by which this disease might cause donor vascular endothelial cell injury (Toyoda 1997). CMV infection may also contribute to endothelial dysfunction and CAV by dysregulation of the endothelial nitric oxide synthase pathway (Valantine 2004). Within the study, CMV infection was categorized as either CMV syndrome (fever for at least 2 days, plus one of the following symptoms: neutropenia, leukopenia, viral syndrome) or CMV disease (systemic disease with CMV organ involvement). In study B253 CMV infection occurred at a reduced rate relative to azathioprine, despite comparable use of CMV prophylaxis in each group (Table 2) (Dorent 2003).

Table 2. B253 Incidence of CMV occurrence through year 1

	Everolimus 1.5 mg/d (n=209)	Everolimus 3mg/d (n=211)	AZA (n=214)
Overall CMV infection	7.7% *	7.6% *	21.5%
CMV disease	1.9%	3.7%	6.5%
CMV syndrome	1.9%	2.8%	4.2%

* p value = 0.001 everolimus vs. AZA

5 Management of everolimus safety

No immunosuppressant agent currently used in cardiac transplantation is fully safe. All drugs in this indication have safety concerns, but must be considered sufficiently effective, given the safety concerns, to be of value in patient management. Safety concerns in this blinded fixed dose everolimus study include an increase in bacterial infections (however, there was neither an increase in death related to infection nor an increase in wound infections) and an increase in triglyceride elevations. These events are well understood by transplant clinicians and specific countermeasure therapy is available to address these complications. However, the most notable complication of combined everolimus and CsA therapy is an increase in average creatinine values, related to a potentiation of CsA nephrotoxicity.

The enhancement of CsA nephrotoxicity is an understood and expected outcome of a blinded trial performed prior to the demonstration of the interaction of everolimus with CsA. The everolimus pivotal studies in heart and kidney transplantation were undertaken prior to the appreciation of how CsA must be managed when dosed with everolimus. Since then, PK/PD analyses demonstrate the significant contribution of CsA to the nephrotoxicity of the regimen.

5.1 Exposure-effect relationships for everolimus and CsA in heart transplantation

Exposure-effect relationships for everolimus and CsA in heart transplantation are similar to those seen in renal transplantation, and demonstrate that: (a) increased CsA exposure increases the risk for renal function impairment (decreased creatinine clearance), (b) in the context of adequate exposure to everolimus, reduced CsA exposure does not increase the risk of rejection.

The PK/PD analyses support a recommendation to reduce CsA dosing. PK/PD analyses indicate reduction in CsA exposure after the 1st 2 weeks of dosing should not increase the propensity for acute rejection (Figure 5). Indeed, observation of cohorts in the study reveal those everolimus patients at the lowest quartiles of exposure for CsA do not have an increased frequency of acute rejection (Figure 7). Similar observations are true in renal transplant; prospectively reduced CsA exposure in renal transplantation produced an acceptable level of acute rejection.

Response surface plots demonstrating exposure-effect relationships of simultaneous CsA and everolimus exposure on the risk of efficacy and renal impairment have been produced to enhance the understanding of the magnitude of the contributions of everolimus and CsA exposure to the overall profile of the combination regimen. The key findings are depicted in Figure 5 and 6:

Figure 5. Response-surface analysis days 15-225 showing reduced risk for acute rejection (y axis) as a function of increased everolimus exposure (x-axis). Cyclosporine exposure (average trough level) Z axis has no effect on rejection within the concentration range tested. (Novartis Data on file)

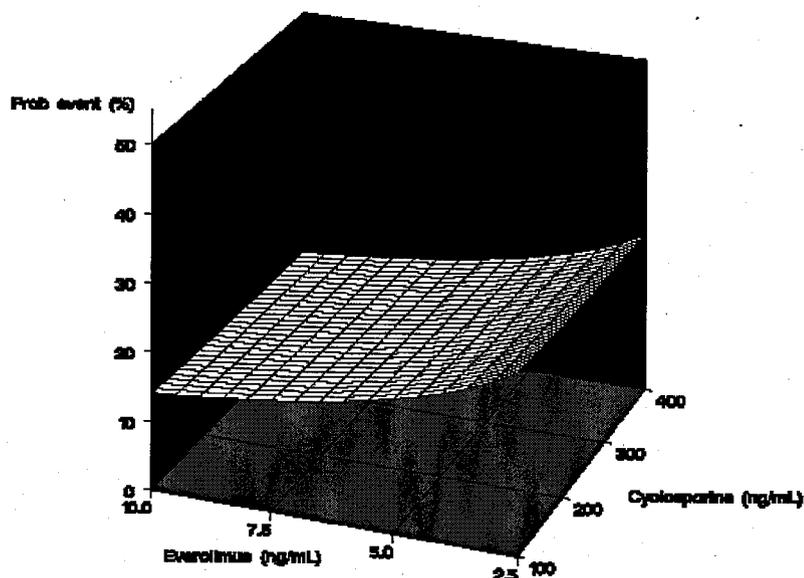


Figure 6. Creatinine Clearance decrease of 30% after month 1 is a function of CsA exposure (average trough levels) (z axis). Everolimus (x axis) demonstrated no effect on the probability of events. (Novartis Data on file)

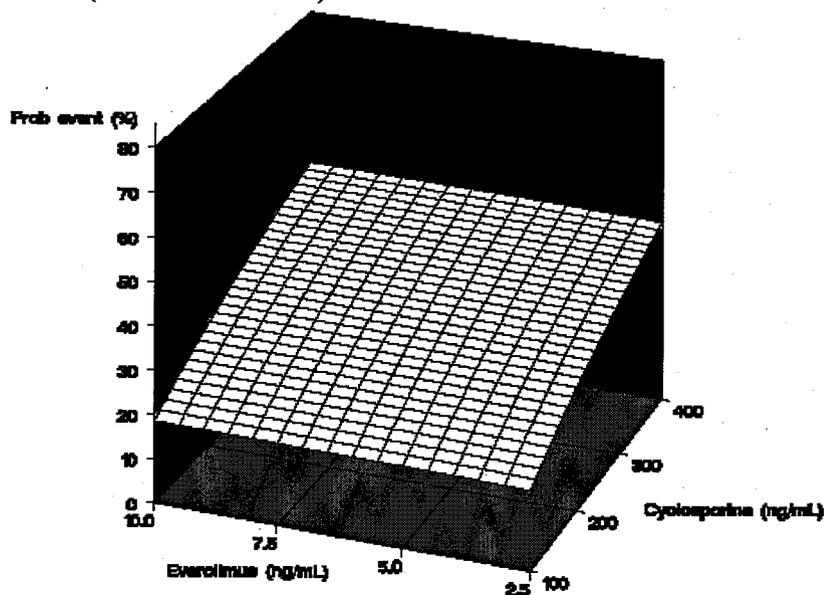
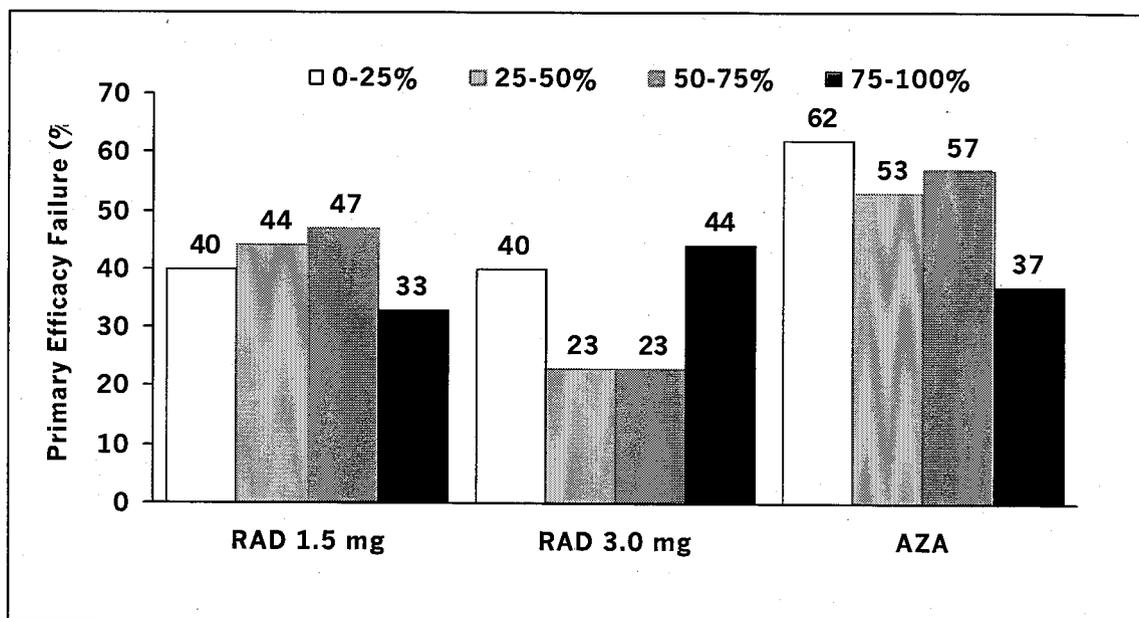


Figure 7. Study B253 Quartile analysis based on CsA exposure Day 1-28. The efficacy failure rates in the everolimus arms were not significantly different at 1 year across the range of average CsA trough levels.



Prospective trials in kidney transplantation provide results consistent with those predicted by the exposure-response models and indicated prospective lowering of CsA is associated with a better overall clinical safety profile and maintained efficacy (Vitko 2004). This provides assurance that reduced CsA exposure in patients treated with everolimus will be accompanied by reduced creatinine.

6 Labeling guidance on everolimus in heart transplant now is preferred to leaving clinicians to unguided use sirolimus out-of-label

Medical need in cardiac transplantation is such that newer agents such as sirolimus are used out of label, without specific guidance, in this indication. However, clinicians experienced in dosing everolimus or sirolimus understand the importance of modifying the CsA dose to prevent renal toxicity. Based upon quartile analysis and PK/PD analysis of everolimus and CSA exposure within the regimen of trial B253, one can conclude it is possible to reduce the overall exposure to CsA and improve renal function without compromising efficacy:

- Initial everolimus dosing at 1.5 mg/day with adjustment to maintain trough levels > 3 ng/mL will be associated with low rates of rejection.
- Exposure-response analyses do not support an influence of CsA on efficacy failure beyond a critical 2 week period. Therefore, dosing with Neoral to achieve protocol-specified CsA trough levels of 250-400 ng/ml during the first month is prudent. This is particularly true as one may need to adjust everolimus dosing with therapeutic drug monitoring to maintain

everolimus trough levels >3 ng/ml and thus assure efficacy is maintained with subsequent Neoral dose adjustments.

- It is important to remember that endomyocardial biopsy at regular intervals is standard procedure at virtually all transplant centers, thus underexposure to CsA in patients in the midst of active rejection is avoided. Conversely, Neoral reduction can be confidently pursued in patients without evidence of rejection on biopsy.
- After month 1 the dosing within the B253 trial suggests cyclosporine trough levels of 200 ng/ml will be sufficiently high to maintain efficacy; after month 6 troughs as low as 100 ng/ml will be acceptable. These levels represent substantial reduction from the mean and median exposure to CsA during the trial, however, the results are sufficient to predict improvement in renal outcomes.

7 Summary

As discussed, there remains substantial unmet medical need in cardiac transplantation – specifically chronic allograft vasculopathy. The use of unlabeled agents in this indication is one means of addressing this issue. However, more desirable to the cardiac transplantation community would be the approval of everolimus in this indication. As noted, no immunosuppressant agent currently used in cardiac transplantation is truly safe, but the safety profile of everolimus is understood and is manageable. The current data available are adequate to guide safe and effective dosing and support the availability of this drug in heart transplantation at this time. That is, the totality of benefits including CAV, acute rejection and reduction of CMV outweighs the risks such that the drug has an overall positive benefit –risk profile. We recognize that the optimal use of all drugs in transplantation evolves over time. Thus, we would support the development of educational materials for prescribing clinicians, careful tracking of patient outcomes, and further studies to ultimately optimize the treatment regimen.

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