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# **Does belatacept improve patient/graft survival after 1 year versus calcineurin inhibitor based regimens?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **Abstract**

**Objective:** The objective of this selective EBM review is to determine whether or not belatacept improves patient/graft survival after 1 year versus calcineurin inhibitors based regimens.

**Study Design:** Review of one randomized controlled trial published in 2010 and two randomized controlled trials published in 2011 were used for this review and selected based on their relevance to the clinical question.

**Data Sources:** Studies were found using PubMed, and Medline Plus.

**Outcomes Measured:** All three studies measured patient/graft survival after 12 months as either a primary or secondary outcome.

**Results:** Vincenti et al (2010) showed belatacept to have a 97% patient/graft survival after 12 months, cyclosporine with 93% patient/graft survival rate. Adverse events (tremors) in this study were noted at 5% for belatacept and 16% for cyclosporine. In Rostaing et al (2011) RCT patient/graft survival was shown as 100% with belatacept and 99% with cyclosporine. Adverse events (pyrexia and pyelonephritis) were calculated to be 20% for belatacept and 19% for cyclosporine. In Rostaing et al (2011) post hoc analysis patient graft survival rates for belatacept were 92.8% and cyclosporine 80.8%. Adverse events in this study were 54.6% for belatacept and 67.2% for cyclosporine.

**Conclusion:** The results of these three RCT are inconclusive as to the efficacy of belatacept over cyclosporine in regards to patient/graft survival after 12 months.

**Key words:** belatacept, calcineurin inhibitors, kidney, renal function

## **Introduction**

Chronic kidney disease affects millions of people worldwide. Lack of affordable healthcare treatment options leads to death for many of these patients.<sup>1</sup> Millions of patients are receiving treatment either from dialysis or a kidney transplant in effort to stay alive. Even though millions are receiving these live saving treatment options there are still many more patients going without treatment for one reason or another.<sup>2</sup>

According to the World Health Organization “in the year 2005, there were approximately 58 million deaths worldwide, with 35 million attributed to chronic disease.”<sup>3</sup> Even after receiving a life saving kidney transplant there are still obstacles that a patient faces to maintain the transplanted organ. Two common causes of death or transplant failure in renal transplant patients include cardiovascular disease and chronic allograft nephropathy.<sup>2</sup>

“There are currently 119,825 people waiting for lifesaving organ transplants in the U.S. of these, 99,261 await kidney transplants.”<sup>4</sup> The cost of kidney disease is straining the US healthcare system. It is estimated that the cost for one year of medical expenses in addition to the kidney transplant itself is approximately \$330,000.<sup>5</sup> Calculations estimate that the cost of treating patients for chronic kidney disease in the US will likely reach \$48 billion per year. To treat just one person with dialysis in the United States it costs over \$50,000.<sup>6</sup> In the United States it is estimated that over \$40 billion was spent in 2009 for the treatment of patients with kidney disease.<sup>7</sup> These costs are only expected to rise higher. Kidney failure patient care accounts for 6.7% of Medicare’s total budget, which translates to less than 1% of the covered population.<sup>1</sup>

Progression into chronic kidney disease is attributed to two other health conditions, diabetes and high blood pressure. Symptoms of chronic kidney disease include fatigue, decreased appetite, insomnia, edema and dry skin. Treatment options for patients with chronic kidney disease include hemodialysis, peritoneal dialysis, renal transplant or medical management with medications such as steroids.

Calcineurin inhibitors are currently the standard of care in renal transplant patients, however these medications can cause nephrotoxicity due to their non-selective nature. Nephrotoxicity can lead to decreased renal function and eventual graft failure. Additionally, calcineurin inhibitors can have a negative effect on other comorbid conditions such as hypertension, diabetes and dyslipidemia.<sup>2</sup> The introduction of belatacept vs. calcineurin inhibitors is an effort to improve renal function and decreased cardiovascular risks the two main reasons for transplant failure or death. Belatacept is a selective costimulation blocker, which is intended to avoid renal and non-renal toxicities such as those seen with the use of calcineurin inhibitors.<sup>2</sup>

This paper evaluates three randomized controlled trials (RCT) comparing the use of belatacept versus calcineurin inhibitors in increasing patient/graft survival 1-year post transplant.

### **Objective**

The objective of this selective EBM review is to determine whether or not belatacept improves patient/graft survival 1-year post transplant versus calcineurin inhibitor regimens.

## Methods

This paper looks at two randomized controlled trials and one post hoc analysis randomized controlled trial. The populations studied in these trials included adult renal transplant patients over the age of 18. The interventions studied were belatacept and cyclosporine. The outcomes measured were patient and graft survival.

The author performed searches using PUBMED and Medline databases using key words belatacept, cyclosporine and renal transplant. All articles were searched in the English language. Each article was published in a peer-reviewed journal. Articles were selected based on clinical relevance to the question addressed above. Inclusion criteria included randomized controlled trials. Exclusion criteria included previous Cochrane reviews. All of the studies used similar statistics to evaluate outcomes, which included numbers needed to treat (NNT) and numbers needed to harm (NNH).

**Table 1 – Demographics of included studies**

Study	Type	#Pts	Age	Inclusion criteria	Exclusion Criteria	W/d	Interventions
Rostaing <sup>8</sup> (2011)	RCT	173	Mean 43-45 years	-CNI-based maintenance immunosuppression stable dosing one-month prior. -cGFR between 35-75 ml/min per 1.73m <sup>2</sup>	-History or recent, recurrent, or severe AR in current allograft or history of graft loss due to AR -Positive T or B cell cross match, a C4d-positive biopsy in current allograft	6	Belatacept regimen 5mg/kg given IV on days 1, 15, 29, 43 and 57 and then every 28 days
Rostaing <sup>9</sup> (2011)	Post-hoc analysis RCT	1209	Mean 53 yrs.	-Diabetic -CNI-based maintenance immunosuppression stable dosing one-month prior. -cGFR between	-History or recent, recurrent, or severe AR in current allograft or history of graft loss due to AR -Positive T or B cell cross match, a	n/a	-Belatacept More Intensive regimen (MI) -Belatacept Less Intensive regimen (LI) -Cyclosporine

				35-75 ml/min per 1.73m <sup>2</sup>	C4d-positive biopsy in current allograft		
Vincenti <sup>1</sup> <sup>0</sup> (2010)	RCT	686	Mean 43	->18 years old receiving a living donor or standard deceased donor kidney transplant	->60 years old -Donors ≥50 years old who had at least two other risk factors(CVA, HTN, and serum creatinine >1.5 mg/dL)	159	Belatacept MI 0-3 months: 10 mg/kg days 1,5; weeks 2,4,6,8,10,12 4-6 months: 10 mg/kg weeks 16, 20, 24 7-12 months: 5 mg/kg every 4 weeks Belatacept LI: 0-1month 10 mg/kg days 1,5; weeks 2,4 2-3 months 10 mg/kg weeks 8, 12 3-12 months 5 mg/kg every 4 weeks

### Outcome

All studies measured patient/graft survival, which included rejection, failure, infection or death.

### Results

This review examined two randomized controlled trials and one post hoc analysis randomized controlled trial comparing the used of belatacept and a calcineurin inhibitor, such as cyclosporine, as a method of immunosuppression following renal transplantation. The study utilized adult patients who had received a kidney transplant with the inclusion criteria cited in Table 1. The data reported in all three studies were dichotomous.

In the Vincenti et al. RCT, 686 patients were used to compare belatacept versus cyclosporine and were included based on the inclusion criteria listed in Table 1.<sup>2</sup>

Exclusion criteria not indicated in Table 1 also included patients who had received any other non-renal solid organ transplants. This study was conducted at 100 centers worldwide. Patients were randomly placed into one of three different study groups. The groups consisted of belatacept low intensity, belatacept high intensity and cyclosporine. The study was blinded to the dosing of the belatacept but open-label to the drug itself. This paper will focus on the low intensity (LI) belatacept regimen versus cyclosporine. The belatacept (LI) dosing regimen is as follows; 0-1 month 10 mg/kg on days 1, 5; weeks 2, 4 then on months 2-3 10 mg/kg during weeks 8 and 12 then on months 3-12 5 mg/kg every 4 weeks. The cyclosporine regimen is as follows; initial daily dose of 4-10 mg/kg then 0-1 month dose adjusted to 150-300 ng/mL then 2-12 months dose adjusted to 100-250 ng/mL. There are three primary outcomes that were being measured in this study, (1) composite patient and graft survival, (2) composite renal impairment endpoint and (3) incidence of acute rejection. The primary outcome of composite patient and graft survival will be the focus of this paper. The primary outcomes were analyzed between the treatment groups using a confidence interval 97.3%, with analysis by intent-to-treat (ITT). The patients receiving belatacept showed a 97% patient/graft survival after 12 months and the patients receiving cyclosporine showed 93% patient/graft survival after 12 months, Table 2. The numbers needed to treat indicate that for every 25 patients treated with Belatacept one more case of graft failure after 12 months will be prevented compared to patients treated with cyclosporine. Adverse events such as tremors were noted in 16% of cyclosporine patients and 5% of belatacept patients, Table 3. The numbers needed to harm indicate that for every 9 patients treated with belatacept 1 fewer would experience an adverse side effect compared to the control group.

In the Rostaing et al RCT, 173 patients were used to compare belatacept versus cyclosporine.<sup>8</sup> The patients were randomly allocated to either belatacept or their current calcineurin inhibitor regimen (cyclosporine or tacrolimus). Belatacept regimen is as follows; 5 mg/kg infusion on days 1,15, 29, 43 and 57, then every 28 days thereafter. The cyclosporine regimen was to maintain trough serum concentration levels of 100-250 ng/mL. Patients included in this study must have had a renal transplant 6 months prior to but no longer than 36 before the enrollment process commenced. Individuals were excluded if they had a history of graft loss due to acute rejection. The data from this study was compiled from 34 different centers in various countries such as the Americas, Europe, Australia and India. The primary outcome measured in this study was the change in glomerular filtration rate from baseline to month 12. Secondary outcomes included patient and graft survival. It is this secondary outcome that will be evaluated in this paper. The data was analyzed with intent-to-treat with a confidence interval of 95%. The experimental belatacept group resulted in no kidney transplant grafts being lost in the first 12 months following transplantation. One patient in the control group died due to complications from a myocardial infarction, but the graft was still functioning at time of death, Table 2. The numbers needed to treat in this study indicated for every 99 patients treated with Belatacept one more case of patient/graft survival after 12 months will be prevented compared to the control. Adverse events were experienced by both the experimental and control groups of this study. Serious adverse events were noted in 24% of belatacept patients and 19% of cyclosporine patients. The two most common serious adverse events noted were pyrexia and pyelonephritis, Table 3. The numbers

needed to harm that were calculated show that 20 patients need to be treated for 1 person to experience a serious adverse event.

In the Rostaing et al. post hoc analysis RCT, 1209 patients were used to compare belatacept versus cyclosporine and were included in the study based on the inclusion criteria as mentioned in Table 1.<sup>9</sup> This paper will examine the effects of belatacept low intensity versus cyclosporine. Patients were randomly selected to be placed into one of three different trial groups; belatacept medium-intensity (MI), belatacept low-intensity (LI) and cyclosporine. This is a post hoc analysis and the dosing regimen has been discussed above. This paper will focus on the belatacept (LI) versus cyclosporine regimen. The experimental group of low intensity belatacept showed a 92.8% patient/graft survival rate after 12 months and the cyclosporine group showed an 80.8% graft survival rate. As indicated in Table 2 for every 9 patients treated with the experimental belatacept one case of patient graft failure after 12 months will be prevented. The total percentage of serious adverse side effects noted were 54.6% for belatacept and 67.2% for cyclosporine, Table 3. The calculated numbers needed to harm, Table 3, show that for every 8 patients treated with belatacept 1 case of a serious adverse event would occur.

**Table 2. Results of treatment efficacy**

Study	CER	EER	RRR	ARR	NNT
Rostaing	0.99	1	0.01	0.01	99
Vincenti	0.93	0.97	0.04	0.04	25
Rostaing (post-hoc)	0.80	0.92	0.14	0.12	9

**Table 3. Results of treatment safety**

Study	CER	EER	RRR	ARR	NNH
Rostaing	0.19	0.24	0.26	0.05	20
Vincenti	0.16	0.05	-0.68	-0.11	-9
Rostaing (post-hoc)	0.67	0.54	-0.18	-0.12	8

### Discussion

Belatacept is an FDA approved immunosuppressant drug used in the prevention of organ rejection.<sup>10</sup> Its use is contraindicated in patients who are Epstein-Barr virus (EBV) seronegative or if their status is unknown.<sup>10</sup> Black box warnings for belatacept include increased risk for post-transplant lymphoproliferative disorder and its use in liver transplant patients is not recommended due to an increase in graft loss and death.<sup>10</sup> This drug has not been studied in patients less than 18 years of age.<sup>10</sup> A limitation of interest is the fact that the studies were open-label to the type of drug being used. However, this open label requirement was necessary to monitor patient's cyclosporine serum levels. Therefore, bias towards a particular drug cannot be ruled out.

### Conclusion

This review of belatacept versus calcineurin inhibitors shows inconclusive results regarding patient/graft survival at 12 months. The numbers needed to treat across the three studies varies from 9 to 99, while the numbers needed to harm range from -9 to 20. Therefore, it is unreasonable to state whether belatacept does in fact improve patient graft survival after 12 months compared to the use of cyclosporine as an immunosuppressant following renal transplantation. An area for further investigation could be to investigate why patients treated with belatacept had an increase incidence of post-transplant lymphoproliferative disorder. According to the University of Iowa Hospital an average

kidney transplant will last 10-12 years.<sup>11</sup> An area of study could be to investigate if belatacept can increase the average length of graft survival.

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