# Belatacept in kidney transplantation - past and future perspectives

## Belatacept no transplante renal - perspectivas passadas e futuras

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## Abstract

Calcineurin inhibitors (CNIs) are used widely for maintenance immunosuppression in renal transplant recipients. However, their side effect profile has led researchers to attempt to find safer alternatives that can maintain effective long-term immunosuppression with less toxicity. Belatacept is a CTLA4-Ig molecule designed to block the costimulatory B7-CD28 signal needed for activation of effector T cells. While it has shown great promise in clinical trials, it has made halting progress towards replacing CNIs in actual clinical practice. The BENEFIT trial revealed some of the advantages of belatacept in terms of maintaining renal function after transplant and reducing some of the metabolic side effects of CNIs related to hypertension and dyslipidemia. Despite that, some cautionary signals have emerged as well, in that belatacept-treated patients experience higher acute rejection rates and greater risk for PTLD. Furthermore, the requirement for monthly intravenous infusions has presented logistical and cost challenges for widespread adoption.

**Keywords:** calcineurin; immunosuppression; kidney transplantation.

## Resumo

Os inibidores da calcineurina (INC) são amplamente utilizados para a imunossupressão de manutenção em pacientes receptores de transplante renal. No entanto, o seu perfil de efeitos colaterais tem levado os pesquisadores a tentar encontrar alternativas mais seguras, que possam manter efetiva imunossupressão de longo prazo com menos toxicidade. O Belatacept é uma molécula de CTLA4-IgG concebida para bloquear o sinal co-estimulador B7-CD28, necessário para a ativação de linfócitos T efetores. Embora tenha demonstrado grande promessa em ensaios clínicos, não tem tido progresso na substituição de INCs na prática clínica. O estudo BENEFIT revelou algumas das vantagens do belatacept em termos da manutenção da função renal após o transplante, e da redução de alguns dos efeitos secundários metabólicos dos INCs, relacionados à hipertensão e dislipidemia. Apesar disso, alguns sinais de precaução também têm surgido, quando doentes tratados com belatacept tem maiores taxas de rejeição aguda e maior risco de DLPT. Além disso, a necessidade de perfusões intravenosas mensais apresenta desafios logísticos e de custo para sua adoção generalizada.

**Palavras-chave:** calcineurina; Imunossupressão; Transplante renal.

## Introduction

For the past sixty years, transplant research has focused on elucidating and targeting pathways involved in T-cell proliferation and signaling. A combinatorial approach have emerged involving different immunosuppressive drugs such as calcineurin inhibitors (CNI), antiproliferative agents (commonly mycophenolate mofetil) and steroids.[1] This strategy has allowed to maximize immunosuppressive effect by blocking different pathways required for T cell activation, while minimizing dose-limiting toxicities from any individual agent. However, researchers have been looking for alternatives to CNIs because of their side effect profile,[2] which include their potential for renal toxicity, hypertension, dyslipidemia and diabetes.

CNI-mediated -nephrotoxicity occurs due to both a direct toxic effect on renal tubules and a vasoconstrictor effect on afferent arteriole, resulting in hypoperfusion

of the glomeruli and a decrease in the glomerular filtration rate (GFR).[3] While the magnitude of the effect seems to be dose- and patient-dependent, the most commonly used doses of CNIs are associated with greater risk of chronic kidney disease.[4]

CNIs also induce hypertension via upregulation of thiazide-sensitive Na-Cl cotransporter in the kidney tubules.[5,6] Patients who discontinue CNIs experience both an acute and a sustained decrease in blood pressure over time.[7] A third major concern with CNIs is the risk of diabetes especially in patients with pre-existing susceptibility to the disease. CNIs directly inhibit insulin production in islet cells of the pancreas,[8] which compounds issues of insulin resistance arising from steroid use in these patients.

## Development of belatacept

In the 1980s, scientists learned that an effective T-cell activation requires an antigen-specific signal through the T-cell receptor (TCR) in combination with simultaneous costimulatory signals. Among these signals, the interaction of B7 ligands expressed on APCs with CD28 on T cells revealed to be a critical step to fully activate T cells.[9,10] In face of challenges in blocking the CD28 receptor, researchers pursued blockade of the B7 ligand on APCs, by developing a fusion protein between CTLA4 and the Fc portion of IgG1.[11] CTLA4 binds with greater affinity to B7 than CD28 and blocks the interaction of B7 with CD28 promoting T-cell anergy.[12,13] In rodent preclinical models, the first generation CTLA4-Ig (abatacept) induced transplantation tolerance.[14-16]

However, this tolerance was not observed in primates due to differences in the binding capacity of CTLA4-Ig and more mature immune system when compared to rodents.[17] Two amino acids were altered in abatacept to produce a new molecule, belatacept, which was found to have higher affinity for the B7 ligands in primates (specifically the B7.2 ligand).[18] While this modification prolonged graft survival in monkeys, it did not induce long-term tolerance as observed in rodents.

## Clinical trials with belatacept in transplantation

The initial phase II trial in kidney transplantation randomized low immunological risk patients at time of transplant to either belatacept or cyclosporine. All patients received induction therapy with basiliximab, mycophenolate mofetil, and corticosteroids. The belatacept group had similar rates of rejection and graft survival that cyclosporine, but the renal function (eGFR) was significantly better at 1 year post-transplantation.[19] In a conversion study, Rostaing *et al.*[20] randomized patients on CNI to either belatacept or continuation of CNI after 6 months of transplantation. The group converted to belatacept had a higher rejection rate (7% *vs.* 0), though GFR was improved at 1 year post-conversion (60.5 *vs.* 56.5 ml/min), suggesting that the renal side effects from CNIs could be in part reversed.

In the phase III BENEFIT trial, 686 patients were randomized at the time of the transplant to either moderate intensity (MI) belatacept, low intensity (LI) belatacept, or cyclosporine, with each group receiving the same basiliximab induction therapy, steroids and mycophenolate mofetil.[21] The study used a combination of deceased and living donors of low immunological risk. The combined primary outcomes included patient and graft survival, renal function, and incidence of rejection. Secondary outcomes were infection rate, cancer incidence, and donor specific antibody development. The 1-,3-, and 5-year results reported sustained superiority of the belatacept arms in terms of renal function; however, statistically significant differences in the co-primary endpoint of patient/graft survival were not observed and there was a higher rate of rejection within first year after transplant in the belatacept groups (22% MI and 17% LI compared to 7% on cyclosporine group).[21-23]

More recently, the 7-year results were reported on approximately 50% of patients who continued enrollment after the original study period of three years.[24] This long-term follow-up has to be interpreted with some caution since it only represents a fraction of the initial patients enrolled, creating a potential selection bias. In any case, the 7-year findings demonstrated a 43% reduction in combined patient and graft survival in the belatacept groups compared to cyclosporine (Table 1).

When patient and graft survivals were analyzed separately, the difference was greater in patient survival than graft survival although, individually, neither of these differences reached statistical significance. Cardiovascular disease was the predominant cause of death in the cyclosporine group (n = 11) compared to the belatacept (n = 6). Whether this lower mortality in the belatacept group is related to less metabolic complications remains to be determined. In regards

**Table 1** Kidney function, graft survival and patient survival with belatacept at 7 years post-transplant

| | Mean eGFR values, ml/min per 1.73 m² of body surface area | | | | | | |
|---|---|---|---|---|---|---|---|
| | Initial Patients | Month 12 | Month 36 | Month 60 | Month 84 | Death-Censored Graft Survival (%) | Patient Survival (%) |
| BENEFIT | | | | | | Month 84 | Month 84 |
| Cyclosporine Group | 215 | 52.5 | 48.6 | 46.8 | 44.9 | 90.2 | 85.6 |
| Low Dose Belatacept | 226 | 66 | 68.9 | 70.3 | 72.1 | 94.6 | 91.8 |
| High Dose Belatacept | 219 | 67 | 68.9 | 70.2 | 70.4 | 95.3 | 90.8 |
| BENEFIT-EXT | | | | | | | |
| Cyclosporine Group | 184 | 40.3 | 38 | 35.8 | 35.3 | 80.7 | 77.6 |
| Low Dose Belatacept | 175 | 47.8 | 50.1 | 52.7 | 54.2 | 86.4 | 73.3 |
| High Dose Belatacept | 184 | 48.3 | 52.5 | 52.2 | 53.9 | 87.6 | 75.1 |

to causes of graft loss, infection was the leading cause in the belatacept groups (n = 3 MI; n = 2 LI *vs*. n = 0 CSA), while thrombosis was most common in the cyclosporine group (n = 1 MI; n = 1 LI *vs*. n = 3 CSA).

The kidney function was significantly better on belatacept groups compared to cyclosporine (Table 1), with a difference of 10 ml/minute seen from the earliest time points after transplant. In addition, over time, the eGFR in the cyclosporine group dropped by about 1 ml/minute/year, whereas eGFR rose in the belatacept group. A difference of about 25 ml/min in renal function in favor of belatacept groups was observed. In regards to safety, there were 3 cases of PTLD in the MI belatacept group, 5 cases in the LI group, and 2 in the cyclosporine group. Other malignancies such as skin cancer and renal cell cancer did not show differences between the groups.

Lastly, it was noticed that the belatacept-treated patients had a significantly lower rate of de novo donor specific antibody generation compared to the cyclosporine group at 7 years post-transplant (1.4% MI and 3.1% LI *vs*. 11.6% in cyclosporine group). One hypothesis is the potential effect of blocking B7:CD28 in plasma cells, which seem to depend on CD28 signal for antibody production.[25] Another hypothesis is that belatacept-treated patients may exhibit greater compliance with its monthly injections.

This finding requires further investigation when compared to tacrolimus since renal function and graft outcomes are known to be better on tacrolimus *vs*. cyclosporine (the control group on all studies with belatacept). In any case, if it holds true, it may indicate a significant advantage, as chronic antibody mediated rejection is universally recognized as a major cause of graft loss. There have been only limited reports assessing the use of belatacept in high immunological risk patients.

Gupta *et al.*[26] reported six patients of whom four had DSAs at the time of transplantation, while 2 had > 80% panel-reactive antibodies. None of the patients developed rejection after conversion from CNI to belatacept and there was an improvement in renal function in all patients ~16 months post-conversion (23.8 ± 12.9 mL/min to 42 ± 12.5 mL/min). Despite those results, further studies are needed to better understand the safety and outcomes of this specific subset of patients.

In a parallel study (BENEFIT-EXT), investigators assessed belatacept use in patients receiving extended criteria donos.[27-30] Similar to the standard criteria donor results, belatacept treated patients had better graft function (about 20 ml/min) at 7 years post-transplant. Interestingly, graft and patient survival were similar comparing belatacept and cyclosporine groups (Table 1). Intuitively, the BENEFIT-EXT population should be the one to benefit the most of a CNI avoidance regimen. Whether the lack of difference is due to the demography of the population, insufficient sample size or follow up time or due to any biological mechanisms is still to be determined.

Also, one could speculate that belatacept would enable transplants of kidneys with higher KDPI because the 20 ml/min superior renal function could be translated in increased graft survival in the long-term. Blood pressure control was better in the belatacept groups compared to cyclosporine (~132 ± 16 compared to 141 ± 22 mmHg systolic) and cholesterol levels (total cholesterol and non-HLD cholesterol) were lower in the belatacept groups, in particular LI, compared to cyclosporine ($p < 0.05$).

## Roadblocks to the widespread use of belatacept

The results of the BENEFIT trial revealed three major concerns. Firstly 8 cases of PTLD were observed in the belatacept groups (n = 445) compared to 2 in the cyclosporine group (n = 221). A post-hoc analysis of this study showed that recipients who developed PTLD in the belatacept group were primarily EBV seronegative.[22] The authors concluded that, because of a lack of immunity to EBV and potent suppression of T cells by belatacept, early EBV infections ran unchecked, causing PTLD via upregulation of oncogenes. Similarly, in the BENEFIT-EXT study 8 cases of PTLD were observed in the belatacept groups (n = 359) compared to one in the cyclosporine group (n = 184). This observation led to the conclusion that patients who were EBV-negative should not be given belatacept (Table 2).

**Table 2** Incidence of rejection and PTLD with belatacept at 7 years post-transplant

| | Initial Patients | Incidence of Acute Rejection % | Cases of PTLD (%) |
|---|---|---|---|
| BENEFIT | | | |
| Cyclosporine Group | 215 | 11.4 | 2 (0.939%) |
| Low Dose Belatacept | 226 | 18.3 | 5 (2.21%) |
| High Dose Belatacept | 219 | 24.4 | 3 (1.37%) |
| BENEFIT-EXT | | | |
| Cyclosporine Group | 184 | 17.3 | 1 (0.54%) |
| Low Dose Belatacept | 175 | 19.5 | 6 (3.43%) |
| High Dose Belatacept | 184 | 21.1 | 2 (1.09%) |

Secondly, a higher rate of acute rejection was observed in the belatacept arms than researchers predicted from the phase II trial.[19] Acute rejection rates were up to two times higher in the MI belatacept arm compared to the cyclosporine arm at 7 years (24% MI *vs*. 11.4% for cyclosporine) (Table 2). In addition, these rejection events were more severe, with predominantly Banff grades IIA and IIB.[21] Indeed, when Emory Healthcare initiated the use of belatacept routinely for all of their kidney transplants, the acute rejection rate was 54% compared to 20% in tacrolimus-treated patients ($p < 0.001$).[31]

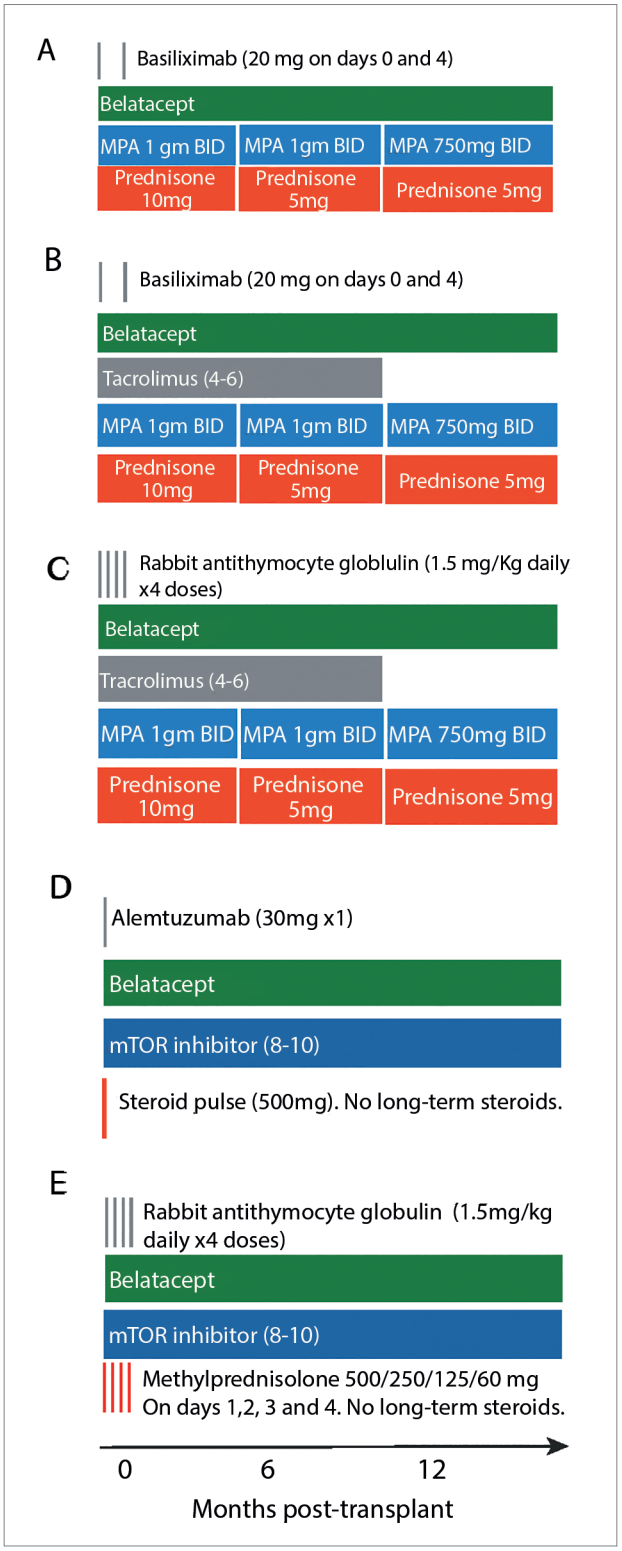
Given the high rate of rejection, the belatacept Emory protocol was adjusted by adding tacrolimus in the first 11 months post-transplant. A retrospective study using registry data from the Scientific Registry of Transplant Recipients (SRTR) revealed that 875 kidney transplant recipients have received belatacept in the USA in 2011.[32] About half of those patients were on concomitant tacrolimus (n = 417) and one quarter received a lymphocyte-depletion induction therapy (n = 262), different than clinical trials. These strategies were associated with lower rejection rates when compared to belatacept alone and non-depleting lymphocyte induction therapy. Interestingly, in the BENEFIT-EXT study, there were no significant differences in the overall incidence of acute rejection among the three groups (Table 2).

Although the increased rates of acute rejection stymied widespread adoption of belatacept since its FDA approval in 2011, novel combination strategies to mitigate the higher rejection of belatacept are emerging with the concomitant use of belatacept with either tacrolimus or mTOR inhibitors and/or the addition of depletion induction therapy (Figure 1).[31,33-35] In other solid organ transplants, belatacept use is still under-investigation.[36-38] A phase II liver transplant trial using belatacept had to be terminated early because of the high rate of acute rejection.[39]

In all belatacept trials a rigorous pretransplant screening for latent tuberculosis was mandated. Yet, data from the two trials indicate that the incidence of tuberculosis was higher among patients receiving belatacept compared to cyclosporine. This finding was observed primarily in countries with higher prevalence of tuberculosis, suggesting that the higher risk of opportunistic infections observed in patients under chronic biological therapy for a variety of diseases may also be observed in kidney transplant recipients receiving belatacept. More data will also be required to learn whether other opportunistic infections, primarily seen in endemic areas such as cryptococcosis, will be more prevalent among patients receiving belatacept. Therefore, high degree of suspicion and continuous monitoring should be advised in these countries.

As the effect size of this new therapy has not been determined yet, a pharmacoeconomic analysis, including infusion costs, is mandatory if this therapy should be incorporated in clinical immunosuppressive protocols. While patients in clinical trials were

**Figure 1.** Traditional and alternative immunosuppressive regimens with belatacept. A, Original regimen proposed on the BENEFIT trials. B, Modified regimen adding tacrolimus in the initial year to lower acute rejection rate from Emory.[31] C, Modified regimen with depletion induction therapy (ATG) and tacrolimus on the initial year post-transplant. D, Modified regimen with alemtuzumab and steroid withdrawal with mTOR inhibitor in place of mycophenolic acid (MPA).[34] E, Modified regimen with ATG and steroid withdrawal with mTOR inhibitor in place of MPA (35). Adapted from.[49]




rigorously monitored, non-compliance in the clinical setting will play a significant role as patients may miss several infusions before next appointment.

## Criticisms of the belatacept trial

One of the criticisms of the belatacept studies is the lack of a contemporary control group, as patients on the control arm received cyclosporine, an outdated CNI, and not tacrolimus that is the CNI of first choice today.[40] Although the authors claimed that graft survival should not differ among CNIs, a randomized trial comparing the standard dose of cyclosporine with low dose tacrolimus showed that graft survival in the group using low-dose tacrolimus was higher than the survival rate of the group that used standard-dose cyclosporine (94% *vs.* 89%, *p-* = 0.01).[41] Furthermore, eGFR was higher in the tacrolimus group than the cyclosporine group. Therefore, belatacept may not have as great of an advantage over tacrolimus compared to the cyclosporine.

Another important detail of the belatacept trial was that no data was included on the dose of mycophenolate mofetil used. According to the trial protocol, patients were initiated on mycophenolate mofetil at a dose of 2 g per day, with dose adjustments at the investigator's discretion. Since cyclosporine inhibits enterohepatic recirculation of mycophenolic acid, the active immunosuppressant in mycophenolate mofetil, it may reduce exposure by 20 to 40%.[42] Thus, even though patients in the three subgroups of the BENEFIT trial were likely administered similar amounts of mycophenolate mofetil, patients in the belatacept subgroups may have been exposed to a significantly larger amount of active immunosuppressant, which could account for differences in the regards to donor-specific antibody development.

The continuous rise of eGFR over time was of concern as well. Early rise in GFR may be due to some hypertrophy of the glomeruli as an adaptation for the single functioning kidney in the recipient, as it is seen in kidney donors that experience a rise of GFR of median ~ 4 ml/min post-donation. However, continued rise in GFR over time suggests adaptive hyperfiltration, which may lead to renal damage in the long-term. Since there is no data on proteinuria in this study (which would help identify hyperfiltration), it is hard to know if this rise in GFR could be deleterious

in the long run. Since the average life of a transplanted kidney is 15 to 20 years and this study was done only over a 7-year period, it is possible that some patients may do well early and poorly thereafter. Further exploration is warranted to better understand this finding.

### Taking belatacept back to the laboratory

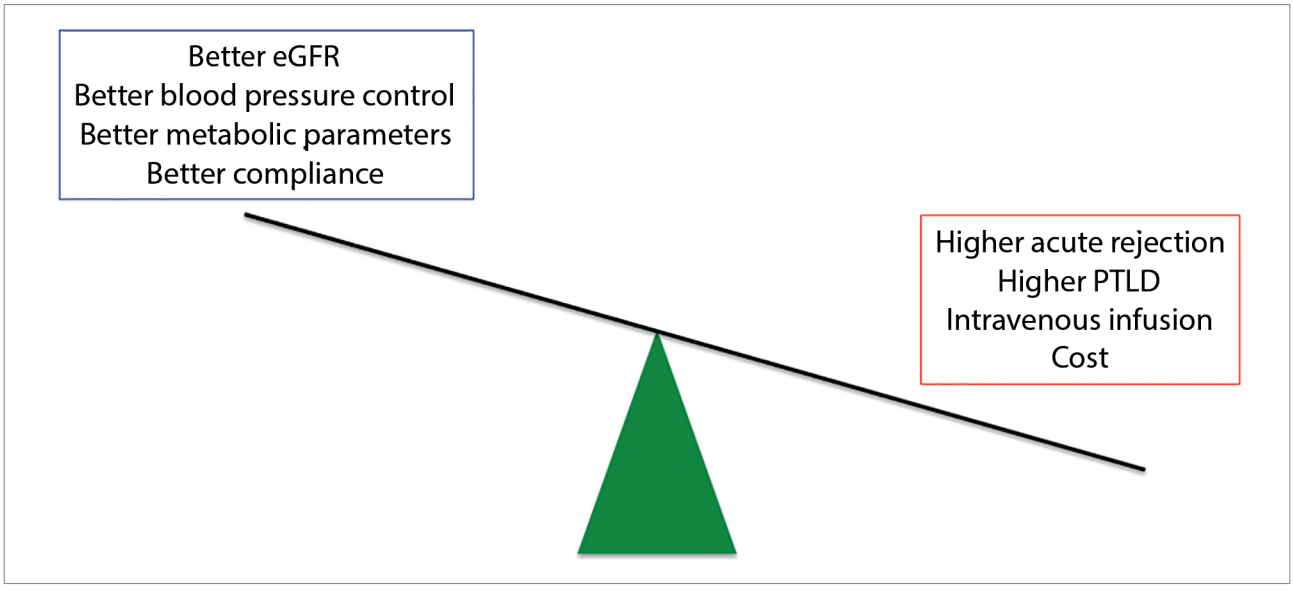
New knowledge about regulatory T cells (Tregs), CTLA4 signaling and CD28-negative T cells led scientists to revisit some unexpected findings upon clinical use of belatacept. As an example, CD28 signaling revealed to be a critical signal for the survival of Tregs, a major regulatory component of the immune system.[43,44] A study in mice which used FoxP3 to track Treg populations concluded that administering CTLA4-Ig reduced the number of Treg cells over time by half and paradoxically accelerated rejection in a single class-II mismatch cardiac transplant model.[45] CTLA4-Ig tipped the ratio of effector T-cells and Tregs towards effector T-cells, leading to the paradoxical response. In addition, CTLA4-Ig also blocks the B7:CTLA4 signal which is an important co-inhibitory pathway both for the function and survival regulatory T-cells.[45,46]

Novel preclinical studies suggests that blocking CD28 receptor may be a more effective strategy with lower rate of rejection in part by not interfering with the CTLA4 coinhibitory signal.[47] A third potential limitation of CTLA4-Ig is the lack of inhibitory effect in T cells that do not express CD28 or that do not require CD28 for activation (eg. Memory T cells). Indeed, Kirk's group have shown that the presence of a subset of cytotoxic CD4 cells which were CD28 negative and CD57 positive prior to transplantation correlated to rejection events in the belatacept-treated patients.[48] However, further validation of this potential biomarker in other centers is still required prior to adoption.

## Conclusion

Immunosuppression in transplantation is evolving and new drugs are being studied to find individualized regimens that may improve patient and graft survival. Belatacept has shown promise in early trials in reducing the metabolic side effects of CNIs and improve graft function. Unfortunately, belatacept is associated with a higher risk of acute rejection (Figure 2). While the mechanisms of these adverse effects remain to be fully elucidated, early results suggest that we may have to judiciously select our patient population in which to use belatacept to optimize outcomes and novel immune biomarkers may help this personalized approach.

**Figure 2.** Advantageous and disadvantages of belatacept use in kidney transplantation.



Using depletion induction therapy and combination with low dose tacrolimus during first year after transplant or mTOR inhibitor are also potential strategies to mitigate the higher rejection. Alas, belatacept is not the panacea once hoped for, but is a solid step in the right direction, and keeps the hope alive for further innovation in targeted immunomodulation in transplantation.

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