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REVIEW

Does belatacept improve outcomes for kidney transplant recipients? A systematic review

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belatacept, calcineurin inhibitor, cyclosporine, immunosuppression, kidney transplantation, tacrolimus.

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Conflicts of interest
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Summary

Background: Belatacept was intended to provide better outcomes for kidney transplant (KT) recipients by allowing minimization/withdrawal of calcineurin inhibitors (CNI) and steroids.

Methods: We searched for randomized controlled trials (RCTs) in adult KT comparing belatacept with CNIs. Methodological quality was assessed. Meta-analyses were performed to calculate odds ratios (OR) and mean differences (MD).

Results: Six RCTs were included. Pooled analyses found no differences for acute rejection at any time point. Renal function [Calculated glomerular filtration rate (cGFR)] was better with belatacept at 12 and 24 months (MD = 11.7 and 13.7 ml/min/1.73 m^2). New onset diabetes after transplantation was lower with belatacept at 12 months (OR = 0.43). Systolic and diastolic blood pressures were lower at 12 months (MD −7.2 and −3.1 mmHg) as were triglycerides at 12 and 24 months (MD = −32.9 and −41.7 mg/dl). Total and low-density lipoprotein cholesterol were lower with belatacept at 24 months (MD = −19.8 and −10.6 mg/dl). There were no differences for other outcomes.

Conclusion: Limited available data suggest a potential benefit for belatacept by reducing the risk of CNI toxicity, especially renal function, without evidence of increased acute rejection. There were no safety issues apart from a possible risk of post-transplant lymphoproliferative disorder in Epstein–barr virus-seronegative recipients. Further studies are required to confirm this benefit.

Introduction

Advances in immunosuppression have led to a reduction in acute rejection rates in kidney transplant recipients along with an improvement in outcomes at 1 year post-transplant [1]. Beyond 1 year, only small improvements have been accomplished and long-term survival of grafts remains virtually unchanged [2]. Main causes of long-term graft loss include chronic allograft injury and death with a functioning graft largely as a result of cardiovascular events or cancer [3].

Current maintenance immunosuppressive regimens usually include a calcineurin inhibitor (CNI). However, CNIs are associated with chronic renal damage and impairment of kidney function. Studies have shown that a reduction in or withdrawal from a CNI can significantly improve renal function [4,5].

T-cell costimulation blockade has been identified experimentally as a potent immunosuppressive process and a possible alternative to CNI therapy [6]. Belatacept is a high affinity variant of CTLA4-Ig and a selective costimulation blocker, which was approved in June 2011 by the US Food and Drug Administration (FDA) for the prophylaxis of rejection in adult kidney transplant recipients. Belatacept is administered during 30-min infusions which can be performed either in an infusion centre or at home [7].

Some early studies in a non-human primate model showed significant benefit to a conventional immunosuppressive combination therapy regimen [8]. Given these findings, clinical trials in humans were undertaken to investigate whether CNI sparing or withdrawal would be possible with belatacept.

Previous nonsystematic reviews of belatacept conducted by Su *et al.* and Martin *et al.* found belatacept to be noninferior to CNI-based therapy [9,10]. The Su review consisted of five trials with a 24-month follow-up [11–15]. The Martin review included the same five trials but included follow-up up to 12 months [11–15]. These two reviews performed systematic literature searches but did not assess bias, include long-term data or formally combine data using a meta-analysis. The aim of this study was to systematically review the available evidence on the efficacy and safety of belatacept as an alternative to CNIs using a meta-analysis where possible.

Methods

This review was prospectively registered with the PROSPERO on 27 September 2013 (registration number CRD42013005771).

Inclusion criteria

Eligible trials included randomized controlled trials (RCTs) in adult kidney transplantation that compared belatacept with a CNI. Kidneys must have been transplanted as a single organ and both living and deceased donors were included. Deceased donors included both standard and extended criteria donors. The primary outcome of interest was acute rejection (AR), and secondary outcomes were renal function (calculated glomerular filtration rate (cGFR), estimated glomerular filtration rate (eGFR), creatinine clearance (CrCl)), patient and graft survival, post-transplant lymphoproliferative disorder (PTLD), new onset diabetes after transplantation (NODAT), hyperlipidaemia, hypertension, malignancies, tuberculosis, progressive multifocal leukoencephalopathy (PML), polyoma virus nephropathy (PVN) and quality of life.

Identification of eligible studies

A systematic literature search was performed up to 10 March 2015 using the Transplant Library (Ovid), MEDLINE (Ovid), Embase (Ovid) and Cochrane's Central Register of Controlled Trials. We searched for ongoing trials from the following sites: ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry (ANZCTR), European Union Clinical Trials register (EUdraCT) and the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP). Search terms for bibliographic databases included all aliases of belatacept combined with MeSH terms and keywords for kidney transplantation. No language restrictions were applied. Where there was more than one report of the same trial, all trial reports were included. Conference abstracts containing data not reported in a full text paper were also included.

Data extraction and methodological quality

Data were independently extracted from eligible trials by two reviewers using a data extraction sheet. Consensus was reached by discussion. Authors were contacted for further clarification when needed. Primary and secondary outcomes were extracted for each available time point. Demographic information was extracted as was the information regarding the immunosuppressive protocol. Funding source for the trial was also recorded.

Methodological quality was assessed independently by the authors using the Cochrane Risk of Bias tool [16]. The risk of bias tool assesses six bias domains, namely selection, performance, detection, attrition, reporting and other sources of bias. We separated blinding into that of patients, investigators and assessors. For each domain, the assessor scored whether there was a high or low risk of bias or whether the risk was unclear. The reviewers also noted whether a sample size calculation was conducted.

Analysis

Continuous and dichotomous trial data were pooled when at least two trials reported an outcome at a common time point using Review Manager (RevMan) Version 5.2. (The Cochrane Collaboration. The Nordic Cochrane Centre, Copenhagen, Denmark). For trials with more than one belatacept arm, a pooled estimate for belatacept was calculated. We calculated odds ratios (OR) for binary outcomes and mean difference (MD) for continuous outcomes including a 95% confidence interval (CI). Heterogeneity between the trials was quantified using the I^2 statistic where we considered $I^2 > 30\%$ as significant. In the absence of heterogeneity, trials were combined using a fixed effects (Mantel–Haenszel) model. In the presence of significant heterogeneity, analyses were performed using the random effects model. If there was significant heterogeneity, outlying trials, which were identified by visual inspection of the forest plot, were removed and a sensitivity analysis was performed with the remaining trials. Potential causes of heterogeneity were also explored by looking for differences between trial participants or interventions. Due to differences in the trial populations, we decided to use the random effects model for all meta-analyses. Publication bias was to be assessed using funnel plots if at least 10 trials

are included [17]. But as only six trials were identified, we did not formally assess publication bias.

Post hoc subgroup analyses were performed to assess whether excluding extended criteria donors from the analysis altered outcomes and to compare outcomes for high-dose versus low-dose belatacept.

Results

Bibliographic searches identified 435 unique references of which six trials met our inclusion criteria (Fig. 1). Six trials, including one reported as an abstract only, were published in 15 journal articles and 116 congress abstracts and included 1731 patients (Table 1) [11–15,18].

Five trials reported on belatacept given from the time of transplantation, that is to *de novo* recipients [11,12,14,15,18], and one trial reported switchover to belatacept between 6 and 36 months post-transplantation [13]. Three of the trials conducted long-term extensions to the original trial period providing data for up to 5 years [19–21]. Five trials compared belatacept with cyclosporine [11,13–15,18], and one trial compared belatacept with tacrolimus [12].

The trial reported by Newell was aborted due to safety concerns, in particular the high incidence of rejection, in patients receiving belatacept [18]. We contacted Dr Larsen who confirmed there had been an error in the 1-year manuscript which erroneously reported 33 AR episodes in the more intensive belatacept arm instead of 32 [14].

Methodological quality

One of the six included trials was published as a congress abstract and hence risk of bias was unclear for all domains (Fig. 2) [18]. The five other trials had a low-to-moderate risk of bias. It was unclear in all reports how the randomization sequence was generated. Four of these five trials reported an adequate method of allocation concealment. None of these trials were double-blinded, but blinding of some form was present in all five trials. Trials used either a

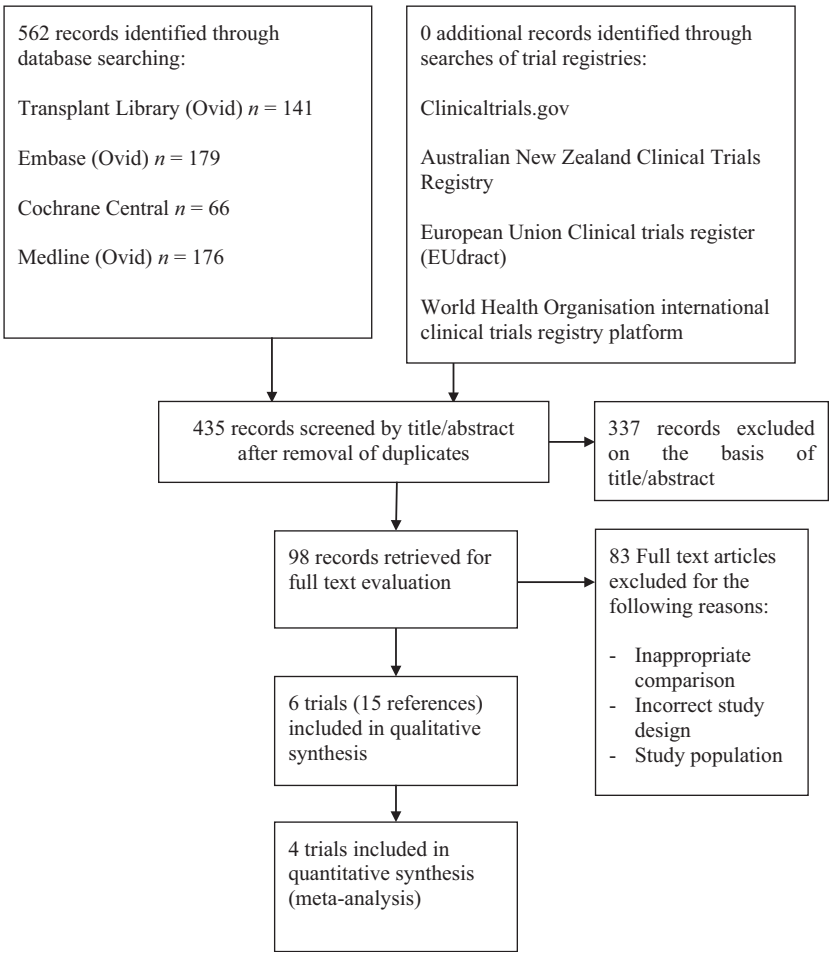

Figure 1 PRISMA flowchart showing inclusion and exclusion of studies during the review process.

Table 1. Characteristics of included studies.

Reference	*N*	Comparison	Belatacept dose	Study period	Recipient gender (M:F) (%) and age (yrs)	Donor type (Living/deceased)	Outcomes
Vincenti BENEFIT [14]	686	Belatacept MI Belatacept LI CsA	Belatacept MI = 0–3 month: 10 mg/kg on days 1, 5 and weeks 2, 4, 6, 8, 10, 12; 4–6 month: 10 mg/kg at weeks 16, 20, 24; 7–12 month: 5 mg/kg every 4 weeks Belatacept LI = 10 mg/kg on days 1, 5 and weeks 2, 4; 2–3 month: 10 mg/kg at weeks 8, 12; 3–12 month: 5 mg/kg every 4 weeks All patients received Basiliximab, MMF and corticosteroids	5 years	464:202 (70%:30%) MI = 44 years LI = 43 years CsA = 44 years	Deceased (42%), living related (42%), living unrelated (16%)	Acute rejection Renal function Patient survival Graft Survivals PTLD NODAT Malignancies Hypertension Hyperlipidemia TB PVN HRQOL
Durrbach BENEFIT Extended Criteria [11]	578	Belatacept MI Belatacept LI CsA	Belatacept MI = 0–3 month: 10 mg/kg on days 1, 5 and weeks 2,4,6,8,10, 12; 4–6 month: 10 mg/kg at weeks 16, 20, 24; 7–12 month: 5 mg/kg every 4 weeks Belatacept LI = 10 mg/kg on days 1, 5 and weeks 2, 4; 2–3 month: 10 mg/kg at weeks 8, 12; 3–12 month: 5 mg/kg every 4 weeks All patients received Basiliximab, MMF and corticosteroids	5 years	366:212 (63%:37%) MI = 57 years LI = 56 years CsA = 56 years	Extended criteria donors	Acute rejection Renal function Patient survival Graft survival PTLD NODAT Malignancies Hypertension Hyperlipidemia PML TB PVN HRQOL
Vincenti Phase 2 Study [15]	218	Intensive belatacept (IB) Less intensive belatacept (LIB) CsA	Intensive B: 0–3 month: 10 mg/kg on days 1, 5, 15, 29, 43, 57, 71, 85; 4–6 month: 10 mg/kg on days 113, 141, 169; 7–12 month: 5 mg/kg every 4 or 8 weeks Less intensive B: 0–1 month: 10 mg/kg on days 1, 15, 29; 2–3 month: 10 mg/kg on days 57, 85; 4–12 month: 5 mg/kg every 4 or 8 weeks All patients received Thymoglobulin induction, MMF and a corticosteroid tapering regimen	5 years	151:67 (69%: 31%) IB = 47 years LIB = 42 years CsA = 46 years	Deceased (73%), living (27%)	Acute rejection Renal function Patient survival Graft survival PTLD NODAT Malignancies Hypertension

Table 1. continued

Reference	*N*	Comparison	Belatacept dose	Study period	Recipient gender (M:F) (%) and age (yrs)	Donor type (Living/deceased)	Outcomes
Rostaing Switchover Study [13]	173	Belatacept Continuation of CNI	Intravenous infusion on days 1, 15, 29, 43, 57 and then every 28 days All patients received MMF, MPA, sirolimus or azathioprine, and steroids	24 months	126:47 (73%:27%) B = 45 years CNI = 44 years	Living or deceased donors (~50%:50%)	Acute rejection Renal function Patient survival Graft survival PTLD NODAT Malignancies Hypertension PML TB PVN
Ferguson Steroid Sparing Study [12]	93	Belatacept (B)+ MMF Belatacept (B)+ sirolimus Tacrolimus (TAC) + MMF	10 mg/kg IV on days 1 and 5, then once every 2 weeks through month 3, every 4 weeks through Month 6 and 5 mg/kg every 4 weeks from Month 7 onward All patients received Thymoglobulin induction	12 months	67:22 (75%:25%) B+MMF = 49 years B+SRL = 53 years Tac+MMF = 54 years	Living related (24%), living unrelated (24%), deceased (52%)	Acute rejection Renal function Patient survival Graft survival PTLD NODAT Malignancies Hypertension Hyperlipidemia
Newell CTOT-10 [18]	19	Tac + alemtuzumab Belatacept + alemtuzumab Belatacept + basiliximab + tac	Dose not reported All patients received MMF	Unknown	–	–	Patient survival Graft survival Rejection Creatinine Renal function

MI, more intensive; LI, less intensive; CsA, Cyclosporine; MMF, mycophenolate mofetil; MPA, mycophenolic acid; SRL, sirolimus; B, belatacept; CNI, calcineurin inhibitor; Tac, tacrolimus; PTLD, post-transplant lymphoproliferative disorder; NODAT, new onset diabetes after transplantation; PVN, polyoma virus nephropathy; TB, tuberculosis; PML, progressive multifocal leukoencephalopathy; HRQOL, health-related quality of life; eGFR, estimated glomerular filtration rate; MO, month.

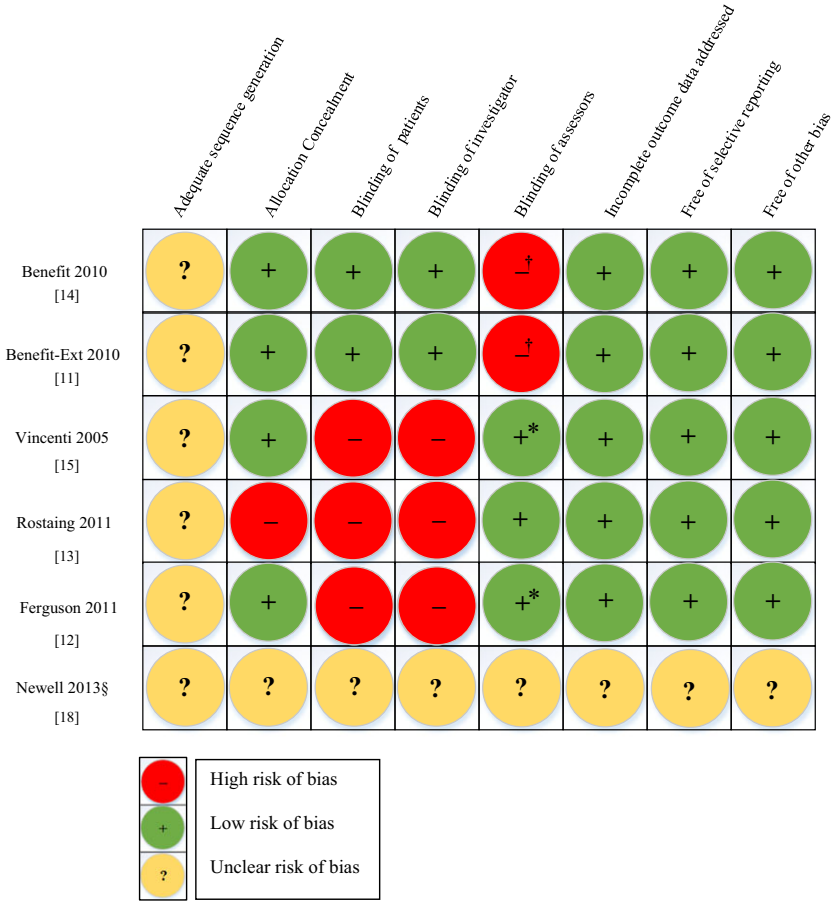

Figure 2 Risk of bias assessment using the Cochrane Risk of Bias tool. §Newell is a conference abstract and therefore risk of bias was unclear for all domains. †Patients in the less and more intensive belatacept regimen were given dummy infusions so they were not aware of which belatacept group they were in. There was no blinding between the belatacept and CNI groups. *Biopsy specimens were sent to a blinded central pathologist to minimize bias in grading for acute rejection however the patients were not blinded.

strict intention to treat analysis for efficacy outcomes [13,15] or a modified intention to treat analysis [11,12,14]. Five trials reported sample size calculations [11–15]. Five of six trials were sponsored by Bristol Myer Squibb [11–13,15,22] and the other by the National Institute of Allergy and Infectious Disease [18].

Acute rejection

At 12 months, the incidence of AR was similar between belatacept and CNIs (four trials, 1516 patients, OR = 1.65, CI 0.83 to 3.30, $P = 0.15$, $I^2 = 64\%$) (Fig. 3). The same effect was found at 24 months (two trials, 1209 patients, OR = 1.77, CI 0.83 to 3.79, $P = 0.14$, $I^2 = 78\%$) and 3 years (two trials, 1209 patients, OR = 1.68, CI 0.87 to 3.25, $P = 0.12$, $I^2 = 73\%$). Heterogeneity was significant for all analyses. We explored whether removal of the outlying trial [15] of the 12-month analysis would reduce the heterogeneity, but it remained significant ($I^2 = 64\%$). Omitting the BENEFIT trial, which showed a large effect in favour of CNI, removed heterogeneity completely ($I^2 = 0\%$)[14]. However, there was still no statistically significant difference in the incidence of acute rejection between the belatacept and CNI groups. The Switchover trial reported no cases of AR in the CNI group versus six cases of AR in the belatacept group at 12 months after switchover [13]. Between 12 and 24 months, there were no further cases in the belatacept group, but three cases of AR in the CNI group.

Newell *et al.* [18] reported five cases (38%) of AR in the belatacept arm with no cases in the CNI arm.

An analysis of the severity of acute rejection episodes shows that most episodes were graded as moderate for both belatacept and CNI-treated patients (Table 2). There were no severe episodes reported for the CNI-treated patients, but three severe episodes were reported for belatacept-treated patients, which were all reported in the BENEFIT trial at 12 months.

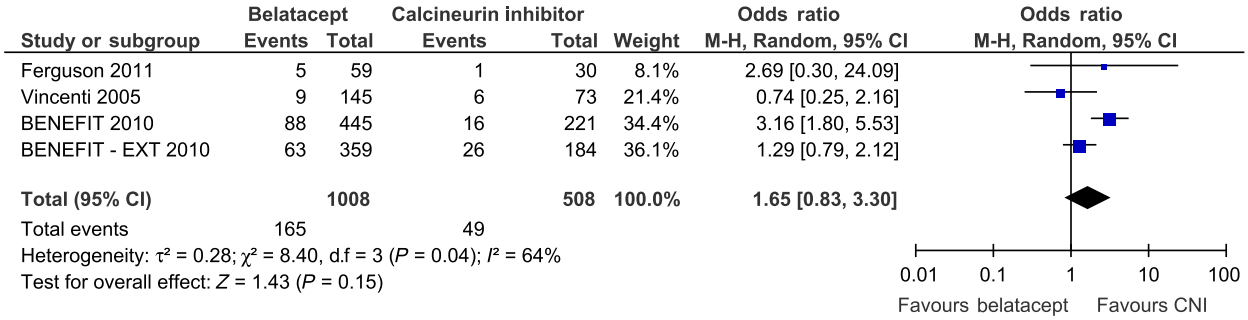

Figure 3 Forest plot to show the odds ratio of acute rejection at 12 months in kidney transplant recipients when treated with belatacept or CNI therapy. Squares represent individual study effects, with the size of the box relating to the weight of the study in the meta-analysis. The diamond represents the summary effect, which was calculated by random effects meta-analysis. A value below 1 favours belatacept and a value >1 favours CNI. Horizontal bars represent 95 per cent confidence intervals. A pooled estimate was calculated for belatacept where there was more than one belatacept arm. CNI, Calcineurin inhibitor.

Patient survival

At 12 months, the rates of patient survival were similar for the belatacept and the CNI groups (four trials, 1516 patients, OR = 1.46, CI 0.61 to 3.5, $P = 0.4$, $I^2 = 35\%$), which was also the case at 24 months (two trials, 1209 patients, OR = 1.67, CI 0.99 to 2.81, $P = 0.06$, $I^2 = 0\%$).

The Switchover trial reported 100% survival in the belatacept group compared with 99% in the CNI group at 12 months [13]. Newell *et al.* [18] reported 100% survival for the belatacept group compared with 83% for the CNI group, but the authors did not state the follow-up period.

Graft survival

At 12 months, the rates of graft survival were similar for the belatacept and the CNI groups (four trials, 1516 patients, OR = 1.20, CI 0.75 to 1.92, $P = 0.44$, $I^2 = 0\%$), which was also the case at 24 months (two trials, 1219 patients, OR = 1.03, CI 0.65 to 1.64, $P = 0.9$, $I^2 = 0\%$).

The Switchover trial reported 100% graft survival for both the belatacept and CNI groups at 12 and 24 months [13,23]. Newell *et al.* [18] reported 77% graft survival for the belatacept groups versus 100% graft survival in the CNI group, but the follow-up period was unclear.

Renal function

Renal function (cGFR) was better for the belatacept groups at 12 months (four trials, 1467 patients, MD = 11.7 ml/min/1.73 m^2, CI 0.09 to 23.35, $P = 0.05$, $I^2 = 97\%$) (Fig. 4), 24 months (two trials, 982 patients, MD = 13.7 ml/min/1.73 m^2, CI 6.34 to 21.10, $P < 0.005$, $I^2 = 78\%$) and 36 months (two trials, 1090 patients, MD = 16.2 ml/min/1.73 m^2, CI 5.39 to 26.94, $P < 0.005$, $I^2 = 94\%$). As heterogeneity was found to be very high, the outlying trial in the forest plot was removed from the 12-month analysis [14]. Removal of the outlying BENEFIT trial eliminated all heterogeneity, although we could not find a plausible explanation for this. The analysis showed that renal function remained significantly improved with belatacept (three trials, 801 patients, MD = 7.4 ml/min/1.73 m^2, CI 4.91 to 9.85, $P < 0.005$, $I^2 = 0\%$).

The Switchover trial showed a mean cGFR of 60.5 ml/min/1.73 m^2 for belatacept patients compared with 56.5 ml/min/1.73 m^2 for CNI patients at 12 months, which changed to 62 ml/min/1.73 m^2 and 55.4 ml/min/1.73 m^2 for the belatacept and CNI arm, respectively, at 24 months [23].

Metabolic outcomes

Metabolic outcomes are summarized in Table 3. The incidence of NODAT was lower with belatacept at 12 months (four trials, 1516 patients, OR = 0.43, CI 0.24 to 0.78, $P = 0.006$, $I^2 = 18\%$). Belatacept therapy resulted in lower systolic (MD = −7.2 mmHg, CI −10.08 to −4.33, $P < 0.005$, $I^2 = 0\%$) and diastolic blood pressure (MD = −3.1 mmHg, CI −4.75 to −1.37, $P < 0.005$, $I^2 = 0\%$). The Switchover trial reported a decrease of 4 mmHg in the belatacept group versus 1.6 mmHg in the CNI group, whilst diastolic blood pressure decreased by 3.5 and 1.7 mmHg for belatacept and CNI groups, respectively. Belatacept groups showed lower total cholesterol (MD = −19.8 mg/dl, CI −28.16 to −11.38, $P < 0.005$, $I^2 = 0\%$) and low-density lipoprotein (LDL) cholesterol (MD = −10.6 mg/dl, CI −18.54 to −2.61, $P < 0.005$, $I^2 = 0\%$) at 24 months. Triglyceride levels were lower for belatacept at 12 months (MD = −32.8 mg/dl, CI −50.17 to −15.47, $P < 0.005$, $I^2 = 35\%$) and 24 months (MD = −41.7, CI −56.27 to −27.04, $P < 0.005$, $I^2 = 46\%$).

The Switchover trial reported that changes in serum lipids were minimal with no significant differences between the groups [13].

Table 2. Incidence of severity of acute rejection episodes according to the Banff 97 criteria.

			CNI						Belatacept				
			Banff 97 grade						Banff 97 grade				
Study	Time point (months)	Number of rejection episodes *N* (*n*)	Mild (1A) *N* (%)	Mild (1B) *N* (%)	Moderate (2A) *N* (%)	Moderate (2B) *N* (%)	Severe (3) *N* (%)	Number of rejection episodes *N* (*n*)	Mild (1A) *N* (%)	Mild (1B) *N* (%)	Moderate (2A) *N* (%)	Moderate (2B) *N* (%)	Severe (3) *N* (%)
De novo belatacept													
Ferguson [12]	12	1 (30)	0	0	1	0	0	5 (59)	0	0	2	3	0
Vincenti [15]	12	6 (73)	1	1	2	2	0	9 (145)	2	0	5	2	0
	60*	–	–	–	–	–	–	6 (102)	0	1	5	0	0
BENEFIT [14]	12	16 (221)	3	5	6	2	0	88 (445)	11	11	33	30	3
	60 - LTE	1 (136)	1	0	0	0	0	1 (320)	0	0	1	0	0
BENEFIT-EXT [11]	12	26 (184)	2	2	17	5	0	63 (359)	4	8	27	24	0
	60 - LTE	0 (87)	0	0	0	0	0	3 (217)	0	1	2	0	0
Newell [18]	'Short term'	0 (6)	0	0	0	0	0	5 (13)	1	0	2	2	0
Late introduction of belatacept													
Rostaing [13]	12	0 (89)	0	0	0	0	0	6 (84)	1	1	3	1	0

*No information provided for CSA arm.

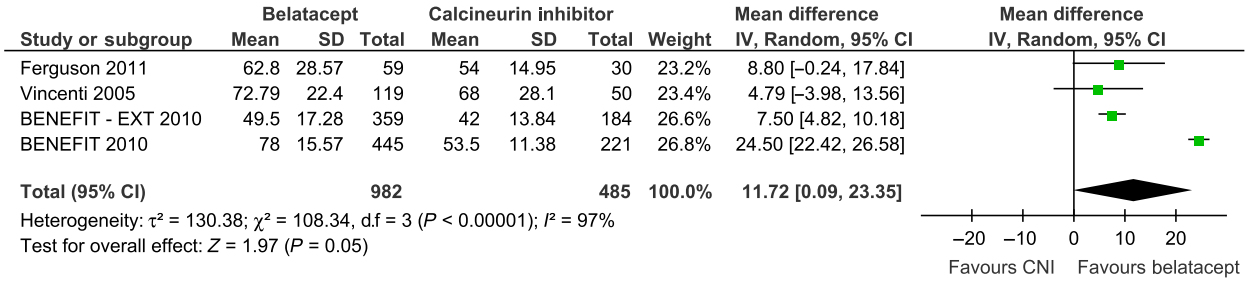

Figure 4 Forest plot to show the mean difference in renal function (cGFR) at 12 months between belatacept and CNI therapy. Squares represent individual study effects. The diamond represents the summary effect from meta-analysis. The summary mean difference was calculated by random effects meta-analysis. A value above 0 favours belatacept. Horizontal bars represent 95 per cent confidence intervals. A pooled estimate was calculated for belatacept where there was more than one belatacept arm. CNI, Calcineurin inhibitor.

Table 3. Pooled estimates of metabolic outcomes and adverse events using random effects meta-analysis.

	Follow-up (months)	Number of trials	Belatacept Mean (SD)	CNI Mean (SD)	MD*	95% CI	*P*	I^2 (%)
Metabolic outcomes								
Systolic blood pressure	12	2	132 (16.7) mmHg	139 (20.0) mmHg	−7.2 mmHg	−10.08 to −4.33	<0.005	0
Diastolic blood pressure	12	2	78 (11.4) mmHg	82 (11.2) mmHg	−3.1 mmHg	−4.75 to −1.37	<0.005	0
HDL cholesterol	24	2	1.7 (17.2) mg/dL	2.4 (29.0) mg/dL	0.2 mg/dL	−2.24 to 2.59	0.89	0
LDL cholesterol	24	2	7.9 (55.6) mg/dL	19.6 (61.8) mg/dL	−10.6 mg/dL	−18.54 to −2.61	<0.009	0
Total cholesterol	24	2	4.9 (56.6) mg/dL	24.6 (63.7) mg/dL	−19.8 mg/dL	−28.16 to −11.38	<0.005	0
Triglycerides	12	2	−14.8 (113.9) mg/dL	19.3 (119.4) mg/dL	−32.8 mg/dL	−50.17 to −15.47	<0.005	35
	24	2	−24.6 (105.4) mg/dL	16.9 (80.4) mg/dL	−4175 mg/dL	−56.27 to −27.04	<0.005	46
			N (%)	*N* (%)	OR†			
NODAT	12	4	32 (3)	36 (7)	0.43	0.24 to 0.78	0.006	18
Adverse events								
PTLD	12	4	9 (1)	1 (0.2)	2.40	0.51 to 11.23	0.26	0
	24	2	9 (1)	1 (0.2)	3.11	0.55 to 17.64	0.20	0
Malignancies‡	12	4	15 (2)	11 (2)	0.63	0.26 to 1.54	0.32	6
	24	2	48 (6)	18 (4)	1.36	0.78 to 2.37	0.28	0
	36	2	23 (3)	13 (3)	0.88	0.44 to 1.78	0.73	0
Skin Cancer	24	2	18 (2)	13 (3)	0.69	0.33 to 1.43	0.32	0
	36	2	26 (3)	17 (4)	0.76	0.41 to 1.43	0.40	0
Tuberculosis	12	2	4 (0.5)	1 (0.2)	0.94	0.03 to 25.46	0.97	57
	36	2	12 (2)	1 (0.2)	4.00	0.72 to 22.12	0.11	0
PVN	36	2	9 (1)	6 (2)	0.68	0.10 to 4.86	0.35	65

N, Number of events; OR, Odds ratio; MD, Mean difference; CI, Confidence interval; PTLD, Post-transplant lymphoproliferative disorder; NODAT, New onset diabetes after transplantation; TB, Tuberculosis; PVN, Polyoma virus nephropathy; LDL, Low-density lipoprotein; HDL, High-density lipoprotein.
*Mean difference of less than zero favours belatacept.
†Odds ratio of less than one favours belatacept.
‡Excluding skin cancer and PTLD.

Adverse events

Adverse events are summarized in Table 3. At 12 and 24 months, there was no significant difference in the incidence of PTLD between the belatacept and CNI groups; however, there was a numerical increase in PTLD, notably with two central nervous system cases in each of the belatacept groups in BENEFIT and BENEFIT-EXT trials by month 36. The BENEFIT trial reported that three of six PTLD cases at 24 months were in patients with Epstein–barr virus (EBV)-negative serology and three of five PTLD cases at 24 months in the BENEFIT-EXT trial had EBV-negative serology. At 36 months, no specific numbers were

given, but according to the authors, the EBV-negative serostatus at the time of transplantation was strongly associated with PTLD in the BENEFIT trial [14]. There were no reports of PTLD from the Switchover trial [13].

Three trials reported the incidence of PML [11–13]. Only one case of PML was reported for the belatacept group in the BENEFIT-EXT trial [11]. Tuberculosis was reported in three trials [11,13,14]. The BENEFIT-EXT trial stated that three of the four tuberculosis cases in the belatacept arm occurred in an endemic area, of which two were from a single site. There were no cases of tuberculosis in the CNI arm. The Switchover trial reported only one case of tuberculosis; this was in the belatacept group [13]. The patient had no previous history of tuberculosis and was living in Mexico.

PVN was reported in three of trials [11,13,14]. In the BENEFIT trial, two and four cases were reported in the belatacept and CNI groups, respectively, whilst in the BENEFIT-EXT trial, seven and two cases for belatacept and CNI groups, respectively, were reported. The Switchover trial reported one case of PVN which was in the belatacept group [13].

Health-related quality of life

Health-related quality of life and side effects were reported for the CNI and low-dose belatacept groups of the BENEFIT and BENEFIT-EXT trials [24]. Both trials showed that belatacept patients had better physical composite scores (PCS) than the CNI groups at 12, 24 and 36 months post-transplant. Absolute PCS differences were small but considered statistically and clinically significant. There was no difference in mental composite scores between groups in either trial. The number of side effects which was assessed by the Modified Transplant Symptom Occurrence and Symptom Distress Scale was lower in the belatacept-treated patients at 12 months (19.2 side effects versus 22.1), 24 months (20 vs. 22.5) and 36 months (19.8 vs. 23).

Long-term extension trials

Vincenti *et al.*, the BENEFIT and BENEFIT-EXT trials reported data up to 5 years (Table 4) [19–21]. In the Vincenti trial, a self-selected population, which was 59% of the original population, who had good outcomes during the original trial entered the long-term extension (LTE) phase. BENEFIT and BENEFIT-EXT patients were eligible for the LTE if they completed the original trial and were deemed appropriate to continue on their assigned therapy, which meant that 68% of the original population entered the LTE in the BENEFIT trial and 53% in BENEFIT-EXT trial.

Meta-analysis was not appropriate for long-term follow-up data as groups can no longer be considered truly

Table 4. Results of long-term extension studies comparing belatacept with CNI.

		Vincenti [15]		BENEFIT [14]		BENEFIT – EXT [11]	
	Follow-up (months)	Belatacept (n = 102)	CNI (n = 26)	Belatacept (n = 320)	CNI (n = 136)	Belatacept (n = 217)	CNI (n = 87)
Efficacy outcomes		Mean cGFR (ml/min/1.73 m^2) ± SD		Mean cGFR (ml/min/1.73 m^2) ± SD		Mean cGFR (ml/min/1.73 m^2) ± SD	
Renal function	60	77.2 ± 22.7	59.3 ± 15.3	75.3 ± 19.0	53.0 ± 17.2	57.6 ± 24.4	44.6 ± 16.4
		N (%)		*N* (%)		*N* (%)	
		Belatacept (n = 102)	CNI (n = 26)	Belatacept (n = 320)	CNI (n = 136)	Belatacept (n = 217)	CNI (n = 87)
Acute rejection	60	6 (6)	0 (0)	38 (12)	9 (7)	3 (1)	0 (0)
Patient survival	60	99 (97)	24 (92)	315 (98)	129 (95)	203 (94)	81 (93)
Graft survival	60	100 (98)	26 (100)	320 (100)	133 (98)	214 (94)	82 (94)
Metabolic outcomes							
NODAT	36	8 (9)	2 (9)	–	–	–	–
	48	8 (9)	2 (9)	–	–	–	–
	60	9 (10)	2 (9)	–	–	–	–
Hypertension	60	12 (12)	6 (23)	–	–	–	–
Adverse events							
PTLD	60	0 (0)	1 (4)	0 (0)	0 (0)	3 (1)	1 (1)
Tuberculosis	60	–	–	3 (1)	2 (2)	1 (0.2)	0 (0)

N, Number of events; CNI, Calcineurin inhibitor; PTLD, Post–transplant lymphoproliferative disorder; NODAT, New onset diabetes after transplantation. In the Vincenti trial, 128 (59%) participants entered the long–term extension (LTE) phase and this was a self–selected population who had good outcomes during the original trial. BENEFIT and BENEFIT–EXT patients were eligible for the LTE if they completed the original trial and were deemed appropriate to continue on their assigned therapy, which meant that 68% of the original population entered the LTE in the BENEFIT and 53% in BENEFIT–EXT trials.

randomized. However, patient demographics in all LTE were similar to those of the corresponding original studies. According to the authors, patients who continued in the LTE also tended to experience better outcomes on their assigned therapy than those who did not enter the LTE [19,20].

Subgroup analysis: more intensive versus less intensive belatacept

Vincenti *et al.*, BENEFIT and BENEFIT-EXT trials included separate arms for more intensive and less intensive belatacept therapy, but pooled analyses found no significant differences between these arms for any of the outcomes (Table 5) [11,14,15].

Subgroup analysis: exclusion of extended criteria donors

In an attempt to pool data for a more homogeneous patient group, we investigated whether exclusion of the BENEFIT-EXT data changed the results [11]. Excluding extended criteria kidneys did not alter the outcomes except for renal function (cGFR) at 12 months which no longer showed a benefit for belatacept (three trials, 924 patients, MD = 13.2 ml/min/1.73 m^2, CI −1.04 to 27.43, $P = 0.07$,

Table 5. Subgroup analysis comparing more intensive versus less intensive belatacept groups using random effects meta–analysis for efficacy outcomes, metabolic outcomes and adverse events.

	Follow–up (months)	Number of trials	MI Incidence *N* (%)	LI	OR	CI	*P*	I^2 (%)
Efficacy outcomes								
Acute rejection	12	2	82 (20)	70 (17)	1.21	0.85 to 1.73	0.29	0
Patient survival	12	3	462 (99)	464 (99)	0.55	0.24 to 1.29	0.17	0
	24	2	385 (96)	386 (96)	0.84	0.41 to 1.70	0.63	0
	36	2	372 (92)	376 (94)	0.81	0.47 to 1.41	0.46	0
Graft Survival	12	3	453 (95)	456 (97)	0.96	0.52 to 1.76	0.89	0
	24	2	378 (94)	378 (94)	0.94	0.52 to 1.71	0.85	0
	36	2	375 (93)	371 (93)	1.11	0.64 to 1.90	0.71	0
			Mean (SD)		MD	CI	*P*	I^2 (%)
Renal function	12	3	66 (22.9) ml/min/1.73 m^2	67 (20.9) ml/min/1.73 m^2	0.13	–2.31 to 2.05	0.91	0
			Incidence *N* (%)		OR	CI	*P*	I^2 (%)
Metabolic outcomes								
NODAT	12	3	15 (3)	15 (3)	0.94	0.35 to 2.52	0.9	28
			Mean (SD)		MD	CI	*P*	I^2 (%)
Triglycerides	12	2	–9.7 (115.9) mg/dL	–19.9 (111.8) mg/dL	8.83	–6.64 to 24.29	0.26	0
	24	2	–24.3 91.8) mg/dL	–24.8 (90.7) mg/dL	0.09	–12.17 to 12.34	0.99	0
Total cholesterol	24	2	4.18 (53.2) mg/dL	5.6 (60) mg/dL	–1.34	–10.32 to 7.63	0.77	0
HDL cholesterol	24	2	2.2 (14.5) mg/dL	1.2 (17.1) mg/dL	1.00	–1.5 to 3.5	0.43	0
LDL cholesterol	24	2	5.2 (52.6) mg/dL	9.8 (58.2) mg/dL	4.60	–14.30 to 5.11	0.35	0
			Incidence *N* (%)		OR	CI	*P*	I^2 (%)
Adverse events								
PTLD	12	3	5 (1)	4 (1)	0.98	0.19 to 4.97	0.98	16
	24	2	5 (1)	5 (1)	0.82	0.17 to 3.82	0.8	15
	36	2	5 (1)	5 (1)	0.99	0.28 to 3.54	0.99	0
Malignancies*	12	3	9 (2)	5 (1)	1.72	0.59 to 4.98	0.32	0
	24	2	10 (2)	13 (3)	0.78	0.21 to 2.91	0.72	55
	36	2	28 (7)	20 (5)	1.38	0.56 to 3.41	0.49	56
Tuberculosis	24	2	6 (1)	6 (1)	1.01	0.23 to 4.35	0.99	31
PVN	36	2	6 (1)	3 (1)	1.93	0.47 to 8.01	0.36	0

N, Number of events; MA, Meta–analysis; OR, Odds ratio; MD, Mean difference; CI, Confidence interval; PTLD, Post–transplant lymphoproliferative disorder; NODAT, New onset diabetes after transplantation; TB, Tuberculosis; PVN, Polyoma virus nephropathy; LDL, Low–density lipoprotein; HDL, High–density lipoprotein; MI, More intensive regimen; LI, Less intensive regimen.
*Excluding skin cancer and PTLD.

I^2 = 93%). However, heterogeneity was very high for acute rejection, renal function, NODAT and patient survival. The remaining outcomes showed low levels of heterogeneity (Table 6).

Discussion

This review has investigated the efficacy and safety of belatacept maintenance therapy in adult kidney transplantation compared with CNI therapy. The limited available data found no significant difference in the rate of AR between belatacept and CNIs groups in *de novo* patients. The secondary outcomes renal function, NODAT, hypertension (systolic and diastolic) LDL cholesterol, triglycerides and total cholesterol levels showed statistically better results for belatacept, but no differences were found for other outcomes. In all cases, the confidence intervals were wide, and therefore, we cannot be sure of the true effect. We investigated high levels of heterogeneity by comparing patient groups and immunosuppressive regimens and removing outlying trials but could not find an obvious explanation.

Better renal function was found in all trials in the belatacept arms. Improved renal function has been shown to be an important factor in long-term graft survival [25]. However, in our analysis, this was not translated to improved long-term allograft and patient survival. Longer term data are needed to evaluate whether improved renal function does result in improved graft and patient survival. The most significant cause of death in kidney transplant recipients is cardiovascular disease, with risk factors being NODAT, hypertension and dyslipidaemia [26]. NODAT is generally found in 10–30% of adults receiving CNI therapy at 12 months [27]. Belatacept significantly reduced the odds of NODAT at 12 months to less than half that of CNI therapy. Hypertension was lower in belatacept patients, as were levels of triglycerides; thus, belatacept seems to improve the cardiovascular risk profile.

A key area of concern associated with belatacept has been PTLD [28]. This was reported in five of the trials with varying levels of reporting on the associated risk factor of EBV status. Previous work has shown the incidence of PTLD to be approximately 1–2% in renal transplant recipients and is highest in the first year post-transplantation in solid organ recipients [28]. The risk factors for early PTLD are EBV seronegativity at the time of transplantation, younger recipients, CMV mismatch or disease and receiving T-cell depleting antibodies. PTLD that occurs later may be due to older recipient age, and duration and type of immunosuppression [28]. The trial by Ferguson, which was conducted most recently, chose to exclude EBV-seronegative patients from their trial population and to use tacrolimus as a comparator rather than cyclosporine [12]. Meta-analysis showed a lower incidence of PTLD in the less intensive belatacept regimen group compared with the more intensive belatacept regimen, but this was not statistically significant. We did not find a significant difference between the belatacept and CNI group nor between the more intensive and less intensive regimen which is likely to be due to the limited number of studies and the low incidence of PTLD.

Suggestions have been made that belatacept increases the risk of PML, tuberculosis and PVN; however, our findings do not support this [7]. BENEFIT-EXT trial reported one case of PML for a belatacept group, and there were no cases across the other trials reporting this outcome. Meta-analysis found no significant difference between belatacept and CNI groups for tuberculosis or PVN.

We also performed a subgroup analysis to compare outcomes of the more intensive dosing regimen of belatacept with a less intensive regimen. These findings suggest that a lower dosing regimen would be equally effective and safe. The lower dosing regimen would result in lower healthcare costs by reducing the direct drug costs, the number of appointments with specialized staff to administer the infusions and the treatment times for patients.

Table 6. Pooled estimates of adverse events for standard criteria donors only using random effects meta–analysis.

			Incidence					
	Follow–up (months)	Number of trials	Belatacept *N* (%)	CNI *N* (%)	OR*	95% CI	*P*	I^2 (%)
Efficacy outcomes								
Acute rejection	12	3	102 (16)	23 (7)	1.84	0.63 to 5.39	0.27	64
Metabolic outcomes								
NODAT	12	3	22 (3)	25 (8)	0.38	0.13 to 1.15	0.09	45
Adverse events								
PTLD	12	3	6 (9)	1 (0.3)	2.07	0.34 to 12.55	0.43	0
Malignancies†	12	3	10 (2)	5 (2)	0.88	0.24 to 3.26	0.85	13

N, Number of events; OR, Odds ratio; CI, Confidence interval; PTLD, Post–transplant lymphoproliferative disorder; NODAT, New onset diabetes after transplantation.

*Odds ratio of less than one favours belatacept.

†Excluding skin cancer and PTLD.

An additional subgroup analysis excluded extended criteria donors from the meta-analysis. This did not alter outcomes except for renal function where the significant benefit observed in the initial meta-analysis was no longer seen. This may indicate that belatacept might have a far more important role in the treatment of recipients of extended criteria kidneys. Heterogeneity was found to be very high after removing the extended criteria donors. It appeared that the results from the BENEFIT trial deviated from the other two trials, and when removed, heterogeneity was no longer present and the effect on renal function was once again observed. This, however, may not be very meaningful as only two trials were pooled in this analysis.

The FDA requested three postmarketing clinical studies to further assess the risks of PTLD and PML. The first study concerns a registry named ENLiST which was developed by Bristol Myer Squibb [29]. The registry will collect data on PTLD and PML that is not currently captured by United Network for Organ Sharing (UNOS). The second study will use the UNOS database and analyse the prescribing pattern of belatacept use in clinical practice. The third study will evaluate rates of PTLD reported in belatacept versus CNI regimens, which will also use the UNOS database. The data from these three studies will be used by the FDA to evaluate risks and ensure correct product labelling. Postmarketing experience previously found regimens involving corticosteroid minimization to be associated with an increased risk of acute rejection, particularly Banff grade III, resulting in graft loss in some patients. As a result, amendments were made to the prescribing information to state that belatacept should be administered in combination with basiliximab induction, MMF and corticosteroids.

The US FDA has issued limitations to the use of belatacept in kidney transplant recipients and states that it should only be given to EBV-seropositive patients and that only the lower dosing regimen should be used [29]. Our findings regarding the risk of PTLD with the use of Belatacept were not conclusive. However, our findings are in agreement with the FDA'a guidance in that the less intensive regimen is as effective to use as the more intensive regimen which may also lead to a lower incidence of PTLD.

Belatacept is administered in 30-min infusions, which are more frequently administered in the initial post-transplant period and changed to monthly infusions during the maintenance phase. In 2011, the estimated monthly cost for the recommended doses of belatacept ranged from $2216 to $4432 depending on the stage of the treatment [30], whilst tacrolimus has a mean monthly cost of $645 for branded or $593 for a generic version [31] Hence, the extra costs of a belatacept regimen compared with a standard tacrolimus regimen are considerable. In addition to the costs, another negative aspect is the need for regular infusions which may be more of a burden to patients compared with taking oral medication. On the other hand, as administration can be controlled when using infusions, better drug compliance can be expected. Another option is to administer belatacept subcutaneously, which has been evaluated by a pharmacokinetic phase 1 trial in healthy subjects [32]. The trial was registered with clinicaltrials.gov in 2007, but no publications could be identified from this trial. However, if proven safe, cutaneous administration is a possible innovation that needs to be further explored [32].

The main limitation of the systematic review is the small amount of data from the few trials meeting the inclusion criteria. We only identified six trials and some of these included small numbers of patients. Further large scale trials would provide much needed data to allow firmer conclusions on the use of belatacept to be drawn.

The limited data available suggest a potential benefit for belatacept in EBV-seropositive patients by allowing CNI minimization or avoidance, thereby reducing the risk of CNI toxicity, without an increased risk of AR. However, further, larger, trials with longer follow-up are required comparing belatacept to a modern tacrolimus-based immunosuppressive regimen in order to confirm this benefit and characterize its safety profile, especially with respect to PTLD. Overall, the cost of the agent and the need for regular infusion (monthly for the life of the graft) should be taken into account when making decisions on its clinical use.

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