A potential drug in the armamentarium of post-cardiac transplantation immunosuppression: belatacept

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Abstract

Undeterred by all the advancement in the field of cardiac transplantation, heart transplant rejection remained its mammoth quandary. Management of heart transplant recipients has drastically improved with current regimens of immunosuppressive drugs. The adverse effects of calcineurin inhibitors are lacking with the use of belatacept, which is a costimulation inhibitor that interferes with the interaction between CD28 on T cells and the B7 ligands on antigen-presenting cells. It was originally approved for use in renal transplant recipients but it has shown promising results in heart transplant recipients.

Keywords Belatacept · Cardiac transplantation · Lung transplant · Immunosuppression

Introduction

Heart transplantation is the last resort for patients with end-stage heart failure (HF) who remain symptomatic in spite of maximal medical and device therapy. Undeterred by all the advancement in the field of cardiac transplantation, heart transplant rejection remained its mammoth quandary [1].

Management of heart transplant recipients has drastically improved with current regimens of immunosuppressive drugs including calcineurin inhibitors. Calcineurin inhibitors are associated with various adverse effects like cardiovascular, metabolic, neurologic, and renal complications that ultimately affect long-term survival in cardiothoracic transplant. Glomerular filtration rate is found to be reduced to even 30 ml by 5 years post-transplant, in about 20% patients [2]. These adverse effects are lacking with the use of belatacept which is a costimulation inhibitor that interferes with the interaction between CD28 on T cells and the B7 ligands on antigen-presenting cells [2, 3].

Bristol-Myers Squibb Company (BMS) got approval by the US Food and Drug Administration (FDA) in June 2011

for belatacept to treat organ rejection in adult kidney transplant recipients [3]. It was originally approved for use in renal transplant recipients, but it has shown promising results in heart transplant recipients. No therapeutic drug monitoring is required and is only administered once a month [4].

Mechanism of action of belatacept

Belatacept is intrinsically a fully human fusion protein of the CTLA4 extracellular domain, having fragments of the Tc domain of human IgG1. It results in the blockade of T cell activation, by binding to CD86/CD80 on the antigen-presenting cell [5, 6].

Abatacept was the first such molecule to inhibit signal-2 with high affinity for CD80/86. It is used in rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis [7]. Belatacept is ten times more potent than abatacept in inhibiting T-cells [8]. It was demonstrated in preclinical studies that anti-B7 antibody therapy might be used as an adjunctive agent for clinical allotransplantation [9]. Another study was performed on combination of monoclonal antibodies specific for CD80, CD86, and CD154 in a mismatched non-human primate renal-allograft model. It was documented in the study that despite the existence of synergy between these agents with respect to T-dependent B cell responses, they could not induce durable tolerance among non-human primates.

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Evidence of belatacept in post-cardiac transplantation and lung transplantation immunosuppression

Cardiac transplantation is the treatment of choice and a life-saving procedure in end-stage heart failure [10].

It was inferred that a decent understanding of the transplant immunology is equitably important, along with the acquaintance of technical aspects of surgery [10, 11]. The immunological outlook of donor and recipients, with regard to heart transplant, was studied in detail by the researchers [12].

Belatacept has shown its potential in maintenance immunosuppression in cardiac transplantation and lung transplantation as documented in previously published studies (Table 1).

Of late, a case report on a female with post-partum cardiomyopathy, who had received an orthotopic heart transplantation, was published by Enderby et al. Patient developed grade 3R rejection for which she was treated with immunosuppressive regimen of tacrolimus (target levels were 8 to 12 ng/mL for the first 6 months after transplantation, with target levels of 6 to 8 ng/mL thereafter), sirolimus (target levels were 4 to 6 ng/mL throughout the whole post-transplant period), mycophenolate mofetil, and prednisone. She eventually developed non-compliance with these drugs and then belatacept was initiated in a dose of 10 mg/kg (750 mg) intravenously on days 0, 7, 14, 28, and for the subsequent 2 months, then 500 mg monthly thereafter. After giving belatacept, biopsies showed negative results for cellular rejection and histologic features of antibody-mediated rejection. Belatacept is administered intravenously at an infusion center, which is different from traditional maintenance medications. This can improve compliance in noncompliant patients [15].

Another case report of an old female, who initially underwent a simultaneous heart-liver transplant (SHLT), was reported by Kumar et al. She had history of transthyretin amyloidosis, chronic kidney disease stage 3B, and amyloid polyneuropathy with chronic hypotension. She became hemodialysis dependent post-transplant, for which she underwent renal transplant after 3 years. She was initiated on induction chemotherapy that consisted of rabbit antithymocyte globulin

6 mg/kg followed by triple-drug immunosuppression including tacrolimus (target level 8–10 ng/mL, which was gradually tapered to 6–8 ng/mL), mycophenolate mofetil (1.5 g/day), and prednisone (tapered to 5 mg/day by 1-month post-transplant). Her post-operative period was again complicated by hypotension and delayed kidney graft function (DGF) despite immunosuppressants. Then, belatacept was initiated (at a dose of 5 mg/kg on days 1, 15, 29, 42, 57 and then monthly) with adequate function of all 3 allografts after 1 year of kidney transplant [16].

A case of a 27-year-old female with congestive cardiac failure, who received a 6-antigen disparate heart transplant, was reported by Austin et al. She faced a complicated post-transplant course. She received daclizumab and methylprednisolone for induction therapy while cyclosporine, mycophenolate mofetil, and a steroid taper were initiated as maintenance immunosuppression. After 2 months, tacrolimus was started (initial trough goal of 8–12 mg/dL, which was reduced afterwards) while cyclosporine was discontinued. Five years post-transplant, mycophenolate was discontinued and sirolimus was started. Abrupt decline in renal function was observed. The patient received renal transplant 6 years post-transplant. After that, belatacept (intravenous infusion of 10 mg/kg during surgery and on post-transplant days 4, 14, 28, 56, and 84, with subsequent doses of 5 mg/kg given every 4 weeks thereafter) was initiated with tacrolimus (twice daily to achieve trough doses 8–12 ng/mL, which was gradually tapered), mycophenolate mofetil (1 g twice daily), and a short steroid taper (methylprednisolone 500 mg I.V. intra-operatively, 250 mg I.V. on day 1, 125 mg I.V. on second post-operative day, and prednisone 5 mg on day 3 and daily thereafter) for maintenance therapy, according to their institutional protocol. Even successful long-term use of de novo belatacept in a young kidney-after-heart transplant recipient has been reported [17].

Promising results of use of belatacept in lung transplantation have also been reported. A case report was presented in bilateral lung re-transplantation in which the patient developed hemolytic uremic syndrome (HUS), attributed to tacrolimus in the third year post-transplant. The patient was

Table 1 Studies mentioning use of belatacept in heart and lung transplantation

Author	Study type	Number of patients	Type of transplant
Iasella CJ et al. [13]	Retrospective	11	Lung transplant
Timofte I et al. [14]	Retrospective	8	Lung transplant
Enderby C Y et al. [15]	Case report	1	Heart transplant
Kumar D et al. [16]	Case report	1	Simultaneous heart-liver transplant (SHLT) and kidney transplant
Austin DS et al. [17]	Case report	1	Kidney-after-heart transplant
Hui C et al. [18]	Case report	1	Lung transplantation

administered sirolimus instead of tacrolimus, but the condition worsened. Then, belatacept was initiated (at a dose of 10 mg/kg I.V. which was then switched to 5 mg/kg for 24 months) and the patient then experienced no episodes of cellular rejection [18].

It has also manifested propitious results in the field of lung transplant. In a single-centered retrospective study on adult lung transplant recipients reported by Iasella et al., eleven lung transplant recipients (LTRs) received belatacept with a mean of 246 days (91–1064) of follow-up after conversion. Two well-defined dosing plans of belatacept were used in the study. The first dosing plan was “conventional dosing” in which belatacept was in a dose of 10 mg/kg on days 1, 5, 15, 29, 45, and 59, followed by 5 mg/kg monthly thereafter. The second strategy was “transitional dosing” that endorsed belatacept in a dose of 5 mg/kg every 2 weeks for the first 6 doses, followed by 5 mg/kg monthly thereafter. It was found that mean estimated glomerular filtration rate was significantly higher in patients after giving belatacept (32.53 vs 45.26, $P=0.04$). Chronic lung allograft dysfunction (CLAD) progression was seen in 2 patients. Overall, 7 patients were alive in the study. There was no significant difference of mean incidence of infections (24.4% vs 16.0%, $P=0.55$) and mean arterial pressure (97.5 vs 92.1 $P=0.38$) [13].

A small retrospective series of lung transplant recipients with acute or chronic renal insufficiency was documented by Timofte et al. The belatacept was initiated in a dose of 10 mg/kg on day 0 and 4, and then on weeks 2 and 4, and (for chronic treatment patients only) then monthly thereafter. They established that use of belatacept permitted safe transient reduction in conventional immunosuppressive therapy and was associated with stable or improved renal function [14].

Current status of belatacept

Belatacept has a crucial role in maintenance immunosuppression [4]. Apart from transplantation of kidney, heart, and lung, it has emerged as a potential frontier in de novo liver transplants, islet cell transplant, and pancreatic transplants [19–22]. This new immunosuppressive candidate can prove to be a milestone in cardiac transplantation. Despite all the benefits of belatacept over calcineurin inhibitors, higher rejection rates have been documented in previous clinical trials [4, 23, 24]. Post-transplant lymphoproliferative disorder is another matter of concern after belatacept treatment. Its incidence was higher among Epstein Barr virus seronegative patients [25].

Conclusion

The present role of costimulatory molecules in governing immune response is promising. The new drug candidate

belatacept is FDA approved for its use in renal transplantation. Its efficacy in cardiac transplantation is yet to be approved and for that, more numbers of randomized clinical trials, on a bigger transplant population, are needed. It is not available in India. There is paucity of data for use of belatacept in cardiac transplantation. Long-term studies in larger population of cardiac transplant recipients are recommended. Post-transplant care is very stringent and pivotal. It should be managed with interprofessional approach.

This drug holds real promise in becoming an important agent for post-transplant maintenance immunosuppression. It may result in improved patient compliance and better long-term survival.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This manuscript represents a review article. Because this project involved no experimental design, the Institutional Review Board approval was not required. Applicable EQUATOR Network (<http://www.equator-network.org>) guidelines were followed.

Statement of ‘human and animal rights’ Not applicable for this review article.

Consent Written informed consent was not required for this review article.

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