

Belatacept: A worthy alternative to cyclosporine?

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INTRODUCTION

Renal transplant is the definitive therapy in patients with end-stage renal disease (ESRD) and offers the only solace for such patients who have no alternative other than frequent hemodialysis, a process which contributes to sufficient morbidity.^[1] Recent developments in the field of renal transplant including novel drugs have contributed immensely to the improvement in 1-year graft survival rates which approach almost 90%.^[2] The pharmacotherapy of organ transplantation for immunosuppression consists primarily of an induction regimen comprising a monoclonal antibody such as basiliximab followed by maintenance immunosuppression consisting of calcineurin inhibitors (CNI) like cyclosporine or tacrolimus, and antiproliferative agents (mycophenolate mofetil) and low-dose corticosteroids. Long-term benefits of these drugs have not been as satisfactory, with the 5-year graft survival falling as low as 72%. Allograft dysfunction is a common cause for allograft loss. Several factors contribute to allograft dysfunction such as interstitial fibrosis, tubular atrophy and chronic toxicity of CNIs.^[3] By the end of 2 years as many as 50% of patients on CNIs develop nephrotoxicity. The increased incidence of cardiovascular diseases in these group of patients have also been attributed to CNI owing to the drug's propensity to worsen hypertension, diabetes and dyslipidemia.^[4-7] An active search for a better alternative to alleviate the suffering of patients on long-term immunosuppressive post renal transplant has led to the development of a new drug belatacept, recently approved by USFDA in June 2011.

MECHANISM OF ACTION

Belatacept is a selective T-cell costimulation blocker. It comprises of a recombinant extracellular domain of human cytotoxic T lymphocyte antigen-4 (CTLA-4) and a fragment of a modified Fc portion of human IgG1. The drug binds to CD 80/86 ligands of antigen-stimulating cells and thereby inhibits the CD-28-mediated T-cell costimulation. T-cells activation requires two signals of which the first signal is mediated by the interaction of major histocompatibility complex (MHC): T cell receptor (TCR) and the second mediated by the costimulatory molecules. The costimulatory molecules CD80/86 ligands in the antigen presenting cells bind to CD28 of the T-cells to induce the immunological response. The costimulatory molecules CD28:CD80/86 interaction is also essential for clonal proliferation of cytotoxic T cells which play a main role in the graft rejection.^[8]

Belatacept has been developed from abatacept by two amino acid substitution (L104E and A29Y).^[9] The mechanism of belatacept is similar to that of abatacept. Abatacept was successful in the treatment of autoimmune conditions like psoriasis and rheumatoid arthritis but was ineffective in preventing renal graft rejection. In contrast to abatacept, belatacept confers higher affinity for CD 80/86 ligands in the APCs and has slower dissociation rates. Thus, belatacept blocks completely the costimulation due to the interaction of CD28 with CD80 and CD86 ligands.^[10] It exhibits a more potent and prolonged inhibition of CD4 and CD8 T-cell proliferation in *in-vitro* studies. Further in studies with nonhuman primates, it confers an effective prophylaxis against graft rejection.

PHARMACOKINETICS

Belatacept is administered as intravenous infusion over 30

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minutes. Dosage regimen consists of four doses of 10 mg/kg body weight during the first month of post-transplantation and further three doses every 4 weeks for the next 3 months of early phase followed by 5 mg/kg body weight administered every 4 weeks during the late phase.^[11] This regimen aims at achieving the steady state earlier by 4 weeks. Belatacept exhibits linear pharmacokinetics and the elimination half-life is around 8-10 days. The clearance of the drug is not affected by hepatic or renal dysfunction. The variability in the pharmacokinetic profile is least and hence therapeutic drug monitoring is not required. Belatacept can be administered with other immunosuppressants like basiliximab, mycophenolate mofetil, and corticosteroids with minimal drug interactions.

CLINICAL TRIALS

The two major phase III trials which led to the approval of the drug were the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) study and the BENEFIT-EXT study. In the BENEFIT study 686 patients were randomized to receive a more intensive belatacept regimen (MI), a less intensive belatacept regimen (LI) or cyclosporine for primary maintenance immunosuppression. Although there was an increase in the incidence of acute rejection episodes in the belatacept groups in the first 3 months, both belatacept regimens had similar patient/graft survival versus cyclosporine (MI:95%, LI:97% and cyclosporine:93%) at the end of 12 months. Belatacept regimens also showed a superior renal function at month 12 as demonstrated by the composite renal impairment end point (MI:55%; LI:54% and cyclosporine: 78%; $P \leq 0.001$ MI or LI versus cyclosporine) as well as the mean measured GFR (65, 63 and 50 ml/min for MI, LI and cyclosporine; $P \leq 0.001$ MI or LI versus cyclosporine).^[12]

These findings were also replicated in another major phase III RCT, BENEFIT-EXT (n=595) with similar arms, which additionally included extended criteria donor kidney recipients who are known to have poor renal function, reduced life expectancy and adverse cardiovascular risk profile. Patient and graft survival were found to be similar in both belatacept and cyclosporine groups. The superiority of belatacept over cyclosporine was also shown by a lesser number of patients in the belatacept arms reaching the composite renal impairment end points and an increase in the mean measured glomerular filtration rate when compared to cyclosporine.^[13]

ADVERSE EFFECTS

The most common adverse reactions with belatacept include anemia, diarrhea, urinary tract infection, peripheral edema, constipation, hypertension, pyrexia, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, and leukopenia.

Serious AEs (SAEs) like post-transplant lymphoproliferative disorder and progressive multifocal leukoencephalopathy are the most worrisome complications during belatacept therapy. At present, belatacept carries a boxed warning for an increased risk of post-transplant lymphoproliferative disorder (PTLD) especially in patients without prior exposure to Epstein Barr virus (EBV).^[14] There is also an increased risk of skin cancer in belatacept users and avoiding unnecessary exposure to sunlight is an important instruction to be given to users of this drug.^[15] The incidence of chronic allograft nephropathy is lesser in patients receiving belatacept. Serious cardiac disorders are less common in belatacept than with cyclosporine.^[16] A comprehensive Risk Evaluation and Mitigation Strategy (REMS), mandated by US FDA, has been devised by Bristol-Myers Squibb, the manufacturer of the drug to ensure that both patients and physicians are well educated about the potential hazards while using this drug so as to minimize the risks incurred. Belatacept evaluated in phase III trials have demonstrated that the recommended regimen is safe and effective for the prevention of acute organ rejection and seems to be well tolerated in majority of the renal transplant recipients compared to cyclosporine.

CURRENT STATUS

The U.S. Food and Drug Administration approved belatacept on June 15, 2011 to prevent acute rejection of kidney transplant in combination with other immunosuppressants like basiliximab, mycophenolate mofetil and corticosteroids in adult patients.^[14] It is marketed under the brand name Nulojix, manufactured by BMS. The drug is not available in India.

LIMITATIONS AND ADVANTAGES

Currently belatacept can be administered only after confirming the patient's prior exposure to EBV. The drug has one more boxed warning on an increased risk of infections and cancers. Hence patients on belatacept should not be given live vaccines as it increases the risk of infection due to immunosuppression. Similarly those on belatacept should avoid exposure to sunlight as it may increase the risk of skin cancer. However, the more disappointing feature of belatacept in the present scenario is the need to be administered in combination with standard immunosuppressants. This may be a possible reason for the occurrence of infections and the unanticipated incidence of PTLD with belatacept. Being a biological agent, the cost of therapy will certainly be higher than the available medication for renal transplant patients once this drug is available in India. However, the improved renal and cardiovascular and metabolic status that has been observed with belatacept in clinical trials might offer nephrologists compelling reasons to prefer it over cyclosporine in future.

CONCLUSIONS

Belatacept, a selective T-cell costimulation blocker offers the possibility of minimizing the toxicity produced by CNIs by its reduced nephrotoxic potential as well as improved cardiovascular and metabolic profile. However, the drug has to be administered by multiple IV infusion and hence requires patients to make frequent hospital visits. This might be a potential restriction in the use of this drug for those patients who are prone to default in the follow-up period. Furthermore one has to ensure that a patient does not have EBV-negative serology to avoid the occurrence of lymphoproliferative disorder. Although clinical trials have shown convincing evidence of its efficacy and safety at the end of 1-year post-transplant, data from long-term follow-up are eagerly awaited to find if all these benefits can be translated into improved long-term survival outcomes and thereby oust cyclosporine from the nephrologist's therapeutic armamentarium for renal transplant patients.

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