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Belatacept

Treatment of Transplant Rejection

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BMS-224818
LEA-029
LEA29Y

CTLA-4 (antigen) [29-tyrosine,104-glutamic acid] (human extracellular domain-containing fragment) fusion protein with immunoglobulin G1 (human monoclonal Fc domain-containing fragment), bimol. (120→120')-disulfide

[Tyr^{29},Glu^{104},Gln^{125},Ser^{130},Ser^{136},Ser^{139},Ser^{148}](CTLA-4 (antigen)-[3-126]-peptide (human extracellular domain-containing fragment) fusion protein with immunoglobulin G1-[233 C-terminal residues of the heavy chain]-peptide (human monoclonal Fc domain-containing fragment)) bimolecular (120→120')-disulfide

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Abstract

Costimulation signals are required for full T-cell activation and they play a vital role in the development of immune responses. The CD28:B7 pathway is the most thoroughly characterized costimulation pathway. Recombinant technology has enabled the development of fusion proteins that competitively inhibit the interactions of both B7 molecules (CD80 and CD86) with their receptors, and belatacept represents the first example of a rationally designed immunosuppressive fusion protein that results in enhanced blockade of a critical T-cell costimulatory pathway. Allogeneic stimulation assays demonstrated the increased inhibition of both primary and secondary T-cell proliferative responses by belatacept compared with the parent compound abatacept. In renal transplant studies performed in rhesus monkeys, a significantly longer median survival time of renal allografts (155 days) was obtained following treatment with belatacept in addition to a regimen of mycophenolate mofetil and methylprednisolone (30 days without belatacept). In a multicenter, randomized, parallel-group phase II study in patients undergoing renal transplantation, the incidence of acute rejection at 6 months was similar between groups who received an intensive regimen of belatacept, a less intensive regimen of belatacept or ciclosporin for primary maintenance immunosuppression. Predefined criteria for the noninferiority of belatacept over ciclosporin were satisfied. In addition, belatacept has demonstrated preliminary efficacy in the treatment of rheumatoid arthritis. It is currently in phase III development for the treatment of kidney transplant rejection.

Introduction

Full T-cell activation requires a costimulation interaction, in addition to an interaction between the T-cell receptor and antigen-presenting cells (APCs), and the importance of costimulation signals in immune responses is widely accepted. As a result, costimulation requirements for T-cell regulation have been extensively studied in the search for novel treatment strategies to control autoimmune diseases, downregulate inflammatory reactions and inhibit allograft rejection (1-3).

The CD28:B7 pathway is the most thoroughly characterized costimulation pathway. CD28 is a transmembrane member of the immunoglobulin superfamily. It is expressed on almost all naive T-cells and is one of the most critical costimulatory receptors for T-cell activation. In contrast, its homologue CTLA4 is considered a negative regulator of T-cell activation, as well as a negative costimulatory molecule. Both molecules share common ligands, the B7 family receptors B7-1 (CD80) and B7-2 (CD86), expressed by APCs (4, 5). By blocking the interaction between these molecules, a state of immune unresponsiveness or tolerance, termed “anergy”, can be achieved (1).

One strategy using recombinant technology has enabled the development of fusion proteins that competitively inhibit the interactions of both B7 molecules with their receptors (6). Belatacept (LEA-29Y, EA-029, BMS-224818) is a second-generation soluble recombinant immunoglobulin fusion protein construct of CTLA4 with improved binding to B7 receptors compared with the parent compound abatacept. It represents the first example of a rationally designed immunosuppressive fusion protein that results in enhanced blockade of a critical T-cell

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costimulatory pathway and is currently in phase III clinical development for solid organ transplant rejection (7-9).

Pharmacological Actions

Equilibrium and kinetic binding analyses demonstrated that belatacept bound with approximately 4-fold increased avidity for CD86 and 2-fold increased avidity for CD80 compared with the parent molecule abatacept (CTLA4-Ig). The equilibrium dissociation constants (K_d) for belatacept were 3.66 and 3.21 nM, respectively, for CD80 and CD86, and the corresponding K_d values for abatacept were 6.51 and 13.9 nM. The increased binding avidity for CD86 was confirmed in cell binding assays using stably transfected Chinese hamster ovary cells. The increased binding potency of belatacept also resulted in a higher functional potency, as demonstrated by more potent inhibition of T-cell costimulation in purified peripheral blood $CD4^+$ T-cells. Primary and secondary allogeneic stimulation assays also demonstrated the increased inhibition of both primary and secondary T-cell proliferative responses by belatacept compared with the parent compound (7).

The inhibition of primary humoral responses *in vivo* by belatacept was investigated in cynomolgous monkeys immunized with sheep red blood cells (SRBCs) within 1 h prior to receiving a single i.v. dose of belatacept. Belatacept inhibited the antibody response to SRBCs in a dose-dependent manner. Doses that resulted in a 50% reduction in the peak anti-SRBC response (ID_{50}) were 0.031 (day 8) and 0.057 mg/kg (day 14); corresponding ID_{90} values were 0.108 (day 8) and 0.17 mg/kg (day 14). These values were 2-3-fold (ID_{50}) and 6-11-fold (ID_{90}) lower than those for abatacept (7).

Renal transplant studies were performed in rhesus monkeys. Belatacept was administered intraoperatively (10 mg/kg i.v.) on day 4 (15 mg/kg i.v.) and on days 14, 28, 42, 56 and 70 (20 mg/kg i.v.), and abatacept (16 mg/kg i.v.) was given intraoperatively and on days 4, 8, 11 and 16. Serum trough concentrations of 18.15-32.41 μg/ml were maintained. The median survival time of renal allografts in recipients treated with belatacept monotherapy (45 days) was significantly longer than that in animals treated with abatacept (8 days), despite comparable serum concentrations. However, all recipients experienced a significant decline in renal function, as indicated by a rise in serum creatinine, between days 20 and 42 posttransplant, although in 2 animals there was a subsequent spontaneous improvement in renal function without additional intervention. When recipients were treated with belatacept combined with conventional immunosuppressive agents in calcineurin inhibitor-free regimens, the median survival in the group treated with belatacept was 155 days versus 30 days in the group treated with mycophenolate mofetil (MMF) and methylprednisolone alone. In addition, recipients treated with a combination of belatacept and a chimeric anti-human IL-2 receptor monoclonal antibody (basiliximab) showed stable serum creatininine and survival of > 100 days, compared with prompt rejection of allografts in recipients treated with basiliximab alone. There were no adverse effects related to the administration of belatacept observed by clinical assessment, laboratory analysis or at necropsy. None of the animals treated with belatacept developed antidonor antibodies during therapy, even when rejection occurred during treatment (7, 10).

Belatacept was evaluated for its potential to prevent islet allograft rejection in a steroid- and calcineurin inhibitor-free regimen in a preclinical primate model. Rhesus monkeys received either the base immunosuppressive regimen (sirolimus and basiliximab) or base immunosuppression and belatacept. Belatacept was administered intraoperatively (10 mg/kg i.v.) and on postoperative day 4 (15 mg/kg i.v.). Additional doses of 20 mg/kg were given on day 14 and every 2 weeks until day 154. The dose and schedule of administration were designed to maintain serum trough belatacept levels at or above 20 μg/ml. Allogeneic islets were transplanted into recipient monkeys via intraportal infusion. Treatment with the belatacept-based regimen significantly prolonged islet allograft survival (56- > 200 days). In contrast, animals that received the base regimen alone rejected the transplanted islets at 7 days. One to two months after the final dose of belatacept, recipients became hyperglycemic. Histological analysis revealed a mononuclear infiltrate, indicating that the loss of glucose control was due to rejection. The belatacept-based regimen prevented the priming of antidonor T- and B-cell responses, as detected by interferon gamma enzyme-linked immunospot and allo-antibody production, respectively (11, 12).

In a further study of islet transplantation in rhesus monkeys, belatacept was shown to significantly increase long-term islet survival when administered in combination with a chimeric antibody targeting CD40 (Chi220, BMS-224819) (172-237 days). Administration of either agent alone resulted in only a modest increase in islet survival (14-84 days) (13-15).

Clinical Studies

A multicenter, randomized, parallel-group phase II study was conducted to demonstrate the noninferiority of belatacept compared to ciclosporin with respect to the incidence of biopsy-proven acute rejection of renal allografts at 6 months. A total of 218 adult renal allograft recipients were randomly assigned to receive an intensive regimen of belatacept (n=74), a less intensive regimen of belatacept (n=71) or ciclosporin (n=73) for primary maintenance immunosuppression. Both belatacept regimens included an early phase (10 mg/kg) and a late phase (5 mg/kg at 4- or 8-week intervals). Doses were dictated by trough profiles shown to be effective in studies of nonhuman primates. The early phase was longer in the intensive regimen (6 months *versus* 3 months) and included more frequent dosing. All patients received induction therapy with basiliximab and adjunctive maintenance therapy with

MMF and corticosteroids. At 6 months, the incidence of acute rejection was similar among the groups: 7% in the intensive belatacept group, 6% in the less intensive belatacept group and 8% in the ciclosporin group. Predefined noninferiority criteria of belatacept *versus* ciclosporin were therefore satisfied. At 12 months, the glomerular filtration rate was significantly higher with belatacept than with ciclosporin, and chronic allograft nephropathy was less common with both regimens of belatacept than with ciclosporin. In addition, lipid levels and blood pressure values were similar or lower in the belatacept group. The results indicated that belatacept provided similar immunosuppressive efficacy to ciclosporin, while showing superiority in terms of cardiovascular and metabolic risk profiles, preservation of kidney function and a lower incidence of chronic allograft nephropathy (16-21).

In a subset of patients in this study at higher risk for reduced long-term allograft function, patient and graft survival at 12 months and the incidence of acute rejection at 6 months were comparable between the groups. The superiority of belatacept over ciclosporin in terms of preservation of kidney function and a lower incidence of chronic allograft nephropathy was also observed in these recipients of suboptimal kidney allografts or those with initial impaired function (22). Furthermore, peripheral blood samples collected between 6 and 30 months posttransplant from 21 patients at 1 center indicated the presence of $CD4^+CD25hi$ T-cells that exhibited the characteristics of regulatory T-cells, similar to those found in healthy donors. These results demonstrated that treatment of kidney transplant patients with belatacept and basiliximab does not prevent the development of regulatory T-cells (23).

The safety and preliminary efficacy of belatacept were evaluated in patients with rheumatoid arthritis who had been treated unsuccessfully with at least one disease-modifying agent. In a randomized, double-blind, placebo-controlled study, 214 patients received i.v. infusions of belatacept (0.5, 2 or 10 mg/kg), abatacept (0.5, 2 or 10 mg/kg) or placebo on days 1, 15, 29 and 57. Ninety-two patients were treated with belatacept. The primary efficacy endpoint was the American College of Rheumatology criteria for 20% (ACR20) improvement on study day 85. Efficacy was dose-dependent, with 34%, 45% and 61% of patients, respectively, treated with 0.5, 2 and 10 mg/kg belatacept meeting these criteria, compared with 31% of patients in the placebo group and 23%, 44% and 53% of patients, respectively, treated with the same doses of abatacept. The incidence of discontinuations due to worsening of rheumatoid arthritis was 3%, 3% and 6% in the respective belatacept treatment groups compared with 31% in the placebo group and 19%, 12% and 9%, respectively, on abatacept. Belatacept infusions were well tolerated at all dose levels and the incidence of adverse events was similar among the treatment groups. No antibodies to belatacept were detected at any time point (24, 25).

Belatacept entered phase III development for the treatment of kidney transplantation rejection in the first quarter of 2005 (8, 9).

Source

Bristol-Myers Squibb (US).

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