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Basiliximab

Prop INN

Immunosuppressant

CHI-621
chRFT5
SDZ-CHI-621
Simulect®

A chimeric CD25 monoclonal antibody constructed from the murine hybridoma RFT5γ2a and chimerized with human IgG1κ that reacts with the IL-2 receptor α-chain

Immunoglobulin G1 (human-mouse monoclonal CHI621 heavy chain anti-human interleukin-2 receptor), disulfide with human-mouse monoclonal CHI621 light chain, dimer

CAS: 179045-86-4

EN: 235373

Introduction

With the approval of cyclic polypeptide ciclosporin in 1983, a new era of success in controlling graft rejection began. While ciclosporin has attained widespread clinical application in organ transplantation procedures, three other drugs were approved: tacrolimus (Fujisawa; 1993), gusperimus (Nippon Kayaku; 1994, in Japan only) and mycophenolate mofetil (Roche; 1995). Two monoclonal antibodies have been launched this year: the humanized monoclonal antibody daclizumab (Zenapax®; Roche) and basiliximab. Two other monoclonal antibodies are advancing in clinical trials, inolimomab (Biotest Pharma) and odulimomab (Pasteur Merieux Connaught).

Because ciclosporin acts by inhibiting the synthesis of a variety of cytokines, particularly interleukin-2 (IL-2), a rational drug combination using agents able to block the IL-2 receptor (IL-2R) has been proposed. Murine monoclonal antibodies to IL-2R had clinical efficacy in preventing acute rejection in renal allograft recipients. However, their use was limited by relatively short disposition half-lives and the rapid development of neutralizing antibodies directed against the heterologous immunoglobulin. The use of chimeric (murine/human) monoclonal antibodies overcame this limitation by reducing immunogenicity. These studies led to the selection of basiliximab for further development (1-3).

Pharmacological Actions

Basiliximab is a chimeric (murine/human) monoclonal antibody (IgG1κ) produced by recombinant DNA technology, that functions as an immunosuppressive agent, specifically binding to and blocking the IL-2R α-chain (IL-2Rα), also known as CD25 antigen, on the surface of activated T-lymphocytes. Based on its amino acid sequence, the molecular weight of the protein has been calculated to be 144 kilodaltons.

Basiliximab functions as an IL-2R antagonist by binding with high affinity (K_a = 1 x 10^{10} M^{-1}) to the α-chain of the high-affinity IL-2R complex and inhibiting IL-2 binding. Basiliximab is specifically targeted against IL-2Rα, which is selectively expressed on the surface of activated T-lymphocytes. This specific high-affinity binding of basiliximab to IL-2Rα competitively inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection (4). Furthermore, unlike previous IL-2R monoclonal antibodies of rat and mouse origin, which were plagued by the rapid development of neutralizing antibodies, basiliximab has reduced immunogenicity as a result of its chimeric origin (5).

Pharmacokinetics and Pharmacodynamics

A clinical study was performed in 37 primary mismatched cadaver kidney transplant recipients in order to study the pharmacokinetics and immunodynamics of basiliximab. The MAb was administered at total doses of 20, 30, 40 or 60 mg, administered as 15- or 20-mg i.v. infusions, with the first dose prior to transplant and later doses administered within the first 10 days after surgery. Daily serum concentrations of monoclonal antibody, analyzed by radioimmunoassay, initially declined in a biphasic manner, with an initial $t_{1/2}$ of 14.4 ± 14.2 h and a terminal $t_{1/2}$ of 13.4 ± 6.0 days. The volume of distribution was 6.9 ± 3.3 l and clearance was 17.4 ± 7.8 ml/h. Based on a study of the concentration-effect (MAb-CD25) relationship, complete suppression of CD25 was achieved at

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MAb concentrations above approximately 0.7 μg/ml. This threshold MAb concentration was reached with all doses of basiliximab administered, although the time of duration above the threshold increased with increasing dosages. A few days after MAb concentration dropped below the threshold, CD25 expression returned to baseline values (5, 6).

Another pharmacokinetic study evaluated the disposition of single-dose basiliximab in 32 recipients of primary mismatched cadaver kidneys. Title compound was administered as a single postoperative dose (40 or 60 mg) by 30-min infusion, in order to determine a single-dose regimen that would be capable of providing IL-2R-saturating serum concentrations over the critical first month posttransplant. Basiliximab was well tolerated, and no patients showed signs of cytokine-release syndrome, hypersensitivity reactions or anti-idiotype antibody response. Peak serum concentrations and AUC increased in a dose-proportional fashion. Concentrations declined in a biphasic manner, and the terminal $t_{1/2}$ was 6.5 ± 2.1 days. Body weight was found to be correlated, albeit only weakly, with both volume of distribution and clearance, although no dose adjustment appears to be needed on the basis of weight. No gender-related differences in disposition of basiliximab were reported. On the basis of previous phase II data and the results obtained in this study, it appears that serum concentrations of more than 0.2 μg/ml are sufficient for purposes of saturating IL-2R epitopes on circulating T-lymphocytes. This threshold concentration was maintained for 26 ± 8 days and for 32 ± 11 days at the doses of 40 and 60 mg, respectively (7-9).

In an open-label phase I/II pharmacokinetic study, basiliximab was administered to 24 adult recipients of orthotopic liver transplants. The drug was given as a total dosage of 40 mg, administered by 30-min i.v. infusion as 4 divided doses of 10 mg (days 0, 2, 4 and 6) or as two doses of 20 mg (days 0 and 4). Again, no adverse hypersensitivity reactions or cytokine-release syndromes were noted. Peak drug concentrations after the first dose were 2.2 ± 0.6 and 3.2 ± 1.0 μg/ml for the 10- and 20-mg dose, respectively. Steady-state volume of distribution, half-life ($t_{1/2}$) and clearance were 10.1 ± 4.1 l, 8.8 ± 9.4 days and 64 ± 18 ml/h, respectively. Baseline CD25 expression (15.1 ± 10.0%) was suppressed completely and consistently for a period of 31 ± 13 days posttransplant in the presence of basiliximab. Ascites fluid drainage and postoperative bleeding were found to account for part of the total body clearance of basiliximab, but did not place the continuity of immunoprophylaxis in jeopardy. Administration of the drug by multiple small doses (4 x 10 mg) did not provide any benefits over the shorter, more compact (2 x 20 mg) dosing regimen (10-12).

Another pharmacokinetic study was performed in pediatric renal transplant patients. Children in this study (aged 2-12 years) were administered the compound as a 12 mg/m^2 i.v. bolus injection prior to transplant and on day 4 posttransplant. Patients were also maintained on ciclosporin microemulsion and steroids. AUC in pediatric patients was 41.3 ± 13.6 μg.day/ml, similar to that in adults (41.2 ± 16.7 μg.day/ml). Clearance in children was half that in adults, however (CL = 20.0 ± 3.5 and 46.2 ± 16.1 ml/h for children and adults, respectively). This was attributed to a smaller distribution volume in children (V_c = 1.7 ± 0.6 l) than in adults (4.9 ± 1.5 l), rather than to differences in $t_{1/2}$ (9.4 ± 4.9 *vs.* 5.8 ± 2.0 days in children and adults, respectively). Receptor-saturating concentrations were maintained in all patients for 29 ± 6 days (13).

Clinical Studies

In a phase I/II efficacy study, basiliximab was administered to 24 recipients of human cadaveric renal transplants. Title compound was given as 6 spaced infusions (day -1 through 24) as escalating doses of 2.5-25 mg. Terminal half-life was 13.1 days, and anti-CD25 activity persisted for up to 120 days. No antibody responses were noted in any of the basiliximab-treated patients. The incidence of rejection was 33%, and initial rejection episodes inevitably occurred during the treatment period. Among patients who did not experience rejection during basiliximab therapy, no rejection occurred over the first year following transplant. Two patients on triple therapy with basiliximab, ciclosporin and azathioprine developed posttransplant lymphoproliferative disorder 9 months after the operation. This disorder did not occur in patients on dual therapy (basiliximab plus ciclosporin). No other viral, fungal or bacterial infections were reported in basiliximab-treated transplant recipients (14).

An efficacy analysis of the 24 liver transplant recipients included in a pharmacokinetic study of basiliximab (11) showed that no rejections occurred in the first 3 months posttransplant, and only 1 patient developed an asymptomatic cytomegalovirus infection; no other infections were reported. Tolerability was excellent. Two basiliximab patients died at 7 and 9 months after transplant, one due to trauma and the other to severe HCV reinfection (15, 16).

In another multicenter, randomized, double-blind, placebo-controlled phase III trial, 41 recipients of primary mismatched cadaveric kidney transplants were randomized to treatment with basiliximab (20 mg on days 0 and 4) or placebo, together with ciclosporin microemulsion (150-200 ng/ml) and low-dose corticosteroids as baseline immunosuppression. The acute tolerability of basiliximab was very good, and no signs of cytokine-release syndrome were observed. Five patients in the placebo group (25%) suffered steroid-resistant acute rejections, whereas no such rejections occurred in the basiliximab group. The incidence of CMV infection during the first year after transplant was 4% in the active treatment group vs. 25% in the placebo arm of the study. Slightly fewer bacterial infections, primarily urinary tract infections, were seen in patients administered the title compound. Patient survival at 24 months was 100% in both groups. Furthermore, the average duration of hospital stay was shortened significantly in the basiliximab group (25 days *vs.* 37 days) (17).

In a large North American multicenter study, 346 renal transplant recipients were treated with basiliximab (40 mg in 2 divided doses of 20 mg on days 0 and 4) or placebo infusions. All patients were also given background immunosuppressive therapy with ciclosporin microemulsion and steroids. A preliminary analysis of 6-month data indicated that rejection episodes had occurred in 35% of the patients treated with basiliximab, as compared to 51% of those on placebo, for an overall reduction in occurrence of rejection episodes of 31%. Nine deaths (4 on active drug and 5 on placebo) and 22 CMV infections (10 on active drug and 12 on placebo) occurred during the first 6-month period. Adverse events were reported by 43% and 51% of patients on basiliximab and placebo, respectively. Acute tolerability was similar in the two treatment arms, and only 1 patient in the study withdrew on the basis of adverse events (18, 19). Patient survival at 6 months was 97-98% in both treatment groups for recipients of both cadaveric and living donor allografts. Graft survival was 97% and 96% for cadaveric and living donor recipients, respectively, in the basiliximab group; graft survival in the placebo group was 93% and 98% for cadaveric and living donor recipients, respectively (20). Further reporting of 12-month results in this study showed that basiliximab, used in combination with ciclosporin microemulsion and steroids, reduces the incidence of acute rejection episodes during the first year after transplantation, with an adverse event profile similar to that of placebo. Benefits were obtained in recipients of cadaveric as well as living donor allografts (21-24).

Another large-scale, double-blind, placebo-controlled phase III study of a similar design (the CHIB 201 international study) was conducted at centers in Europe and Canada for purposes of evaluating the efficacy of basiliximab in preventing acute rejection episodes in renal allograft recipients. A total of 380 adult recipients of mismatched cadaveric kidney allografts were administered basiliximab (40 mg in 2 divided doses) or placebo in addition to ciclosporin microemulsion and steroids. A 6-month interim analysis for this study indicated that acute rejection episodes had occurred in 32.7% and 51.2% of the patients administered active drug and placebo, respectively, representing a 36% reduction in rejection episodes. Eleven deaths were reported in the 6-month analysis and 14 at the 12-month analysis. Basiliximab was well tolerated, with no cases of cytokine-release syndrome. The incidence of serious adverse events was similar in the two treatment arms (54.7% and 55.4% on basiliximab and placebo, respectively) (23, 25-28).

Basiliximab has also been shown to be effective in the treatment of renal allograft recipients with diabetes mellitus, a high-risk group in which allograft survival remains inferior in spite of important advances in immunosuppressive therapy. A meta-analysis was made of two large phase III trials in which patients were randomized to treatment with basiliximab (40 mg in 2 divided doses) or placebo, again in combination with ciclosporin microemulsion and steroids. These studies included 80 diabetics and 283 nondiabetics in the basiliximab treatment groups and 70 diabetics and 289 diabetics in the placebo groups. Graft survival was superior among diabetic patients treated with basiliximab as compared to placebo, with only 3 grafts (4%) lost on active treatment as compared to 10 (14%) on placebo. Graft loss among nondiabetics, in contrast, was similar in the two treatment arms (10% for basiliximab *vs.* 9% for placebo). Overall, basiliximab reduced the incidence of acute rejection epidoses and provided superior immunoprophylaxis and graft survival among adult diabetic patients receiving a first renal transplantation (29, 30).

Basiliximab (Simulect®) has been approved for marketing in Switzerland and the U.S. where it is indicated for the prophylaxis of acute organ rejection in de novo renal transplantation in combination with ciclosporin and corticosteroid-based immunosuppression. It is supplied as vials containing lyophylized powder, 20 mg, plus a solvent ampule containing 5 ml water for injection (31-33).

Manufacturer

Novartis Pharma, Inc. (CH).

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