Drugs 1999 Feb; 57 (2): 207-213
0012-6667/99/0002-0207/$07.00/0

Basiliximab

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Abstract

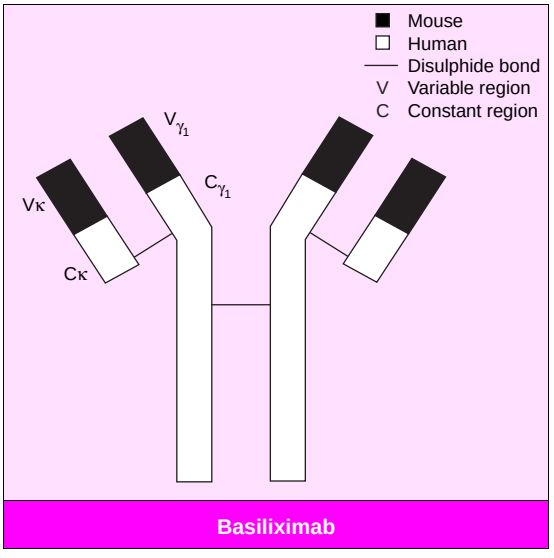
▲ The chimaeric monoclonal antibody basiliximab specifically binds the α subunit of the interleukin-2 (IL-2) receptor on activated T lymphocytes. Through competitive antagonism of IL-2, basiliximab supplements standard immunosuppressive therapy after renal transplantation.

▲ ≤24 hours after a single intravenous dose of basiliximab 2.5 to 25mg, ≈90% of available IL-2 receptors on T lymphocytes were complexed with the drug. This level of basiliximab binding was maintained for 4 to 6 weeks when renal transplant patients received basiliximab 20mg 2 hours before and then 4 days after transplantation surgery.

▲ In 2 large, well-designed trials, the percentage of patients with biopsy-confirmed acute rejection episodes after renal transplantation was significantly lower with basiliximab 20mg (administered 2 hours before and then 4 days after transplantation surgery; 30 or 33%, respectively) than placebo (44 or 46%) at 6 months after surgery.

▲ Basiliximab was well tolerated during clinical trials. The incidence of infections (including active cytomegalovirus infection) and post-transplant lymphoproliferative disorders was similar with basiliximab and placebo. Cytokine release syndrome was not observed in patients who received basiliximab.

Features and properties of basiliximab (CHI 621, chRFT5)	
Indication	
Prevention of acute renal transplant rejection	
Mechanism of action	
Inhibition of interleukin-2 (IL-2) stimulated T lymphocyte proliferation	Mouse-human chimaeric antibody specific for the IL-2 receptor α subunit
Dosage and administration	
Recommended dose	20mg
Concomitant therapy	Cyclosporin microemulsion and corticosteroids
Route of administration	Intravenous (20 to 30 min infusion)
Frequency of administration	2 hours before and on day 4 after renal transplantation surgery
Pharmacokinetic profile (single infusion of basiliximab 15 to 25mg)	
Peak 24h plasma concentration	≈12 mg/L
Plasma concentration necessary to saturate IL-2 receptors on T lymphocytes	≥0.2 mg/L
Clearance	0.017 L/h
Terminal elimination half-life	13.4 days
Adverse events	
Most frequent	Infection (incidence similar with basiliximab and placebo)
Serious events	Post-transplant lymphoproliferative disorder or malignancy (rare)



Acute rejection occurs during the first year after transplantation surgery in 30 to 50% of patients who receive kidneys from living or cadaveric donors with ≥1 human leucocyte antigen (HLA) mismatch.[1-3] Although acute rejection episodes frequently respond well to treatment with high-dose corticosteroids or antilymphocyte antibodies, their occurrence is associated with a significant reduction in graft survival rates ≥5 years after transplantation.[1-3]

The standard therapies for prevention of acute rejection episodes in renal transplant recipients are double (cyclosporin and corticosteroids) and triple immunosuppression (cyclosporin, corticosteroids and azathioprine).[4] Basiliximab is a chimaeric mouse-human monoclonal antibody which supplements these standard immunosuppressive therapies. Other supplemental therapies available include antilymphocyte antibodies (muromonab CD3 and antithymocyte and antilymphocyte globulins),[4,5] daclizumab,[6,7] tacrolimus[4,8] and mycophenolate mofetil.[4,9]

1. Pharmacodynamic Profile

Mechanism of Action

• The proliferation of activated T lymphocytes is an essential step in the development of acute transplant rejection episodes, and is normally triggered when the cytokine interleukin-2 (IL-2) binds to the multisubunit IL-2 receptor present on this cell type.[10] Basiliximab binds with high specificity and affinity to the α subunit (also known as Tac antigen or CD25) of the IL-2 receptor.[11] When complexed with basiliximab, IL-2 receptors on T lymphocytes are not available for IL-2 binding, and proliferation of the associated cells is inhibited.[11]

• As shown in figure 1, basiliximab concentrations ≥1 mg/L inhibited >90% of IL-2 binding to an IL-2 receptor-expressing T lymphocyte line *in vitro*.[12] Serum concentrations of basiliximab ≥1 mg/L are readily achieved in renal transplant patients (see section 2).[11,13,14]

• Basiliximab saturated IL-2 receptors quickly *in vivo*. Approximately 90% of IL-2 receptors on peripheral T lymphocytes were not available for IL-2 binding ≤24 hours after renal transplant recipients received a single intravenous dose of basiliximab 2.5 to 25mg.[11,13]

• The duration of IL-2 receptor saturation with basiliximab in adults was 4 to 6 weeks when a dose of 20mg was administered 2 hours before and then on day 4 after renal transplant. As shown for a representative patient in figure 2, ≈90% of IL-2 receptors on peripheral T lymphocytes were not avail-

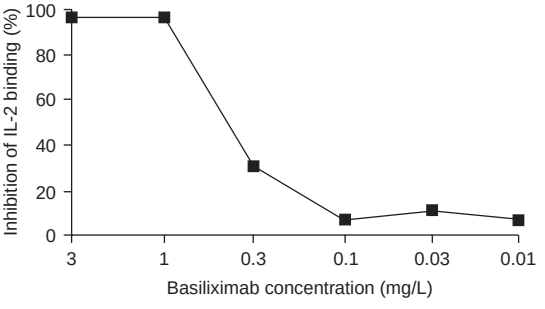


Fig. 1. Effect of basiliximab on interleukin-2 (IL-2) binding to IL-2 receptors *in vitro*. Binding of radiolabelled recombinant human IL-2 to an IL-2 receptor-expressing T lymphocyte line, MT4, was inhibited ≈5 to 95% by basiliximab 0.01 to 3 mg/L. X-axis scale is not proportional. Reproduced with permission from Novartis Pharmaceutical Corporation.[12]

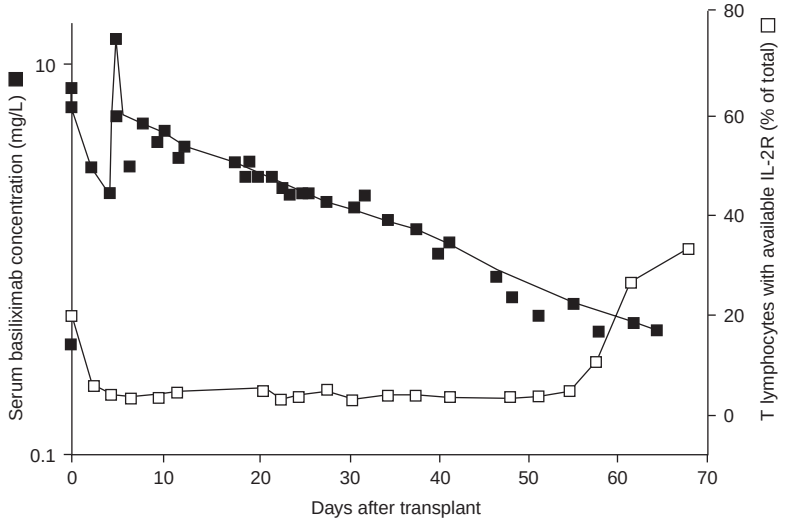


Fig. 2. Availability of interleukin-2 (IL-2) receptors on peripheral T lymphocytes and corresponding serum basiliximab concentrations in a representative patient who received basiliximab 20mg 2 hours before (day 0) and on day 4 after renal transplantation. At the indicated time-points, the percentages of peripheral T lymphocytes with IL-2 receptors available for IL-2 binding were measured by flow cytometry and serum basiliximab concentrations were measured by enzyme-linked immunosorbent assay.[12] **IL-2R** = IL-2 receptors.

able for IL-2 binding for 30 to 45 days after patients received basiliximab.[12,15]

- The duration of IL-2 receptor saturation with basiliximab was 29 days in paediatric renal transplant recipients (8 patients aged 2 to 12 years) when basiliximab 12 mg/m^2 was administered 2 hours before and on day 4 after surgery.[16]

Other Effects on the Immune System

- The expression of IL-2 receptors on T lymphocytes did not appear to change with basiliximab administration in renal transplant recipients. Basiliximab 2.5 to 25mg did not down-regulate IL-2 receptor expression on circulating T lymphocytes when administered 2 hours before and on days 2, 6, 11, 17 and 24 after transplantation.[11]

- Basiliximab selectively affected activated T lymphocytes in renal transplant recipients. There were no significant differences in total peripheral lymphocyte or lymphocyte subset (natural killer cell and B, T helper, cytotoxic T and δ-positive T lymphocyte) counts or in the numbers of T lymphocytes expressing activation markers during compared with after IL-2 receptor saturation in patients who received basiliximab 2.5 to 25mg (a total of 6 infusions administered 2 hours before and on days 2, 6, 11, 17 and 24 after transplantation).[11]

- As predicted for a mouse-human chimaeric monoclonal antibody, basiliximab was minimally immunogenic. 1 (0.4%) of 246 renal transplant recipients developed human antibodies directed against the variable regions of basiliximab (anti-idiotype antibodies) 3 to 5 months after administration of the drug (total doses of 15 to 150mg given over periods of 1 to 4 weeks after transplantation).[17]

2. Pharmacokinetic Profile

- Serum concentrations of basiliximab [measured by radioimmunoassay (RIA)] generally ranged from 5 to 10 mg/L immediately after a single infusion of 15 or 20mg of the drug in renal transplant recipients.[13] Serum basiliximab concentrations declined over time in a biphasic manner (fig. 2).[12] Peak 24 hour serum basiliximab concentrations (measured by RIA) were generally proportional to

dose in the range 2.5 to 15mg, but appeared to plateau at ≈12 mg/L with the 15 and the 25mg dose.[11]

- IL-2 receptor saturation was achieved with serum basiliximab concentrations of ≥0.2 mg/L [measured by enzyme-linked immunosorbent assay (ELISA)][14,15] and 0.7 or 1 mg/L (measured by RIA)[11,13] in adult renal transplant recipients and ≥0.2 mg/L (measured by ELISA) in paediatric renal transplant recipients.[16]

- The volume of distribution (Vd) of basiliximab in the central compartment was reported to be 3.1[13] or 4.9L[14] in adults and 1.7L in children.[16] Vd did not correlate with bodyweight in adult patients (r = 0.29).[14]

- Clearance was 0.017 L/h with 1 to 3 infusions of basiliximab 15 or 20mg[13] and 0.046 L/h with a single dose of 40mg in adult renal transplant recipients.[14] Consistent with reduced Vd, clearance was 0.02 L/h in paediatric patients who received an infusion of basiliximab 12 mg/m^2 2 hours before and on day 4 after renal transplantation.[16] Clearance was not well correlated with bodyweight in adults (r = 0.45)[14] or with bodyweight, age or body surface area in children.[16]

- The terminal elimination half-life ($t_{½\beta}$) of basiliximab in renal transplant recipients was reported to be 13.4 days in adults (with basiliximab 15 or 20mg 2 hours before, then 1 or 2 times in the 10 days after surgery[13] and 9.4 days in children (with 12 mg/m^2 of the drug 2 hours before and on day 4 after surgery).[16] These values for $t_{½\beta}$ are markedly longer than the value reported for the mouse monoclonal antibody muromonab CD3 (1 to 2 days).[5]

3. Therapeutic Trials

The efficacy of basiliximab in the prevention of acute rejection has been evaluated in 2 multicentre, double-blind, randomised, placebo-controlled trials in Europe and Canada[18,19] and the US.[15,20,21] A total of 722 first-time recipients of renal transplants from cadaveric[15,18,20,21] or living donors[15, 20,21] with ≥1 HLA mismatch participated in the trials; they were representative of the local patient populations.[18,20] Basiliximab 20mg or placebo was administered as a 30-minute intravenous infusion 2 hours before and on day 4 after surgery, and all patients received concomitant double immunosuppressive therapy (cyclosporin microemulsion and prednisone) throughout the study period. Both trials used an intent-to-treat analysis.

- The incidence of acute rejection episodes was significantly lower with basiliximab than placebo in both studies in the first 6 months after transplantation from cadaveric and living donors (fig. 3). The incidences were 30 or 33%, respectively, with basiliximab and 44 or 46% with placebo.

- At 12 months after transplantation, the percentages of patients with clinically diagnosed acute

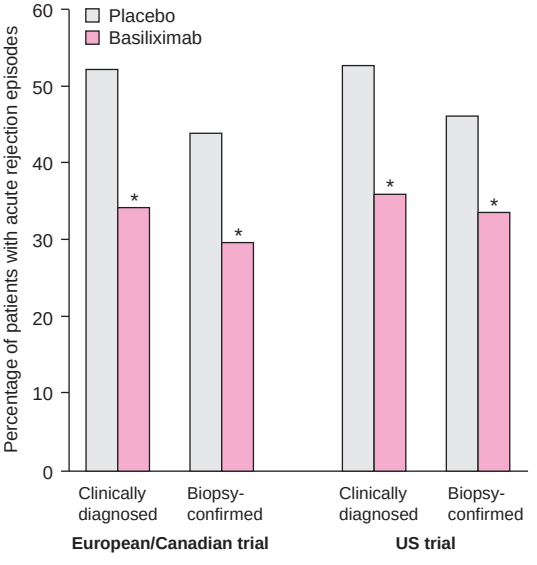


Fig. 3. Therapeutic efficacy of basiliximab in the first 6 months after transplantation surgery with renal allografts from cadaveric and living donors. Placebo or basiliximab 20mg, were administered 2 hours before and on day 4 after transplantation surgery to 186 and 190 patients in the European/Canadian trial (all donors were cadaveric)[18] and to 173 patients in each treatment group in the US trial (30% of donors were living and 70% were cadaveric),[20,21] respectively. **clinically diagnosed** = rejection episodes identified on the basis of clinical data; **biopsy-confirmed** = rejection episodes confirmed by examination of biopsy specimens; * $p \leq 0.017$ *vs* placebo.

rejection episodes continued to be significantly lower with basiliximab (38% in both trials) than placebo (55% in both trials; $p \leq 0.002$).[18,20] When only biopsy-confirmed acute rejection episodes were considered, the incidence was 35% with basiliximab and 49% with placebo at the 12-month time-point in the US trial.[20]

- Overall graft survival rates (range 87 to 95%), patient survival rates (95 to 97%) and the histological severity of rejection (graded using the Banff criteria)[22] were similar at 12 months after transplantation in renal transplant recipients with basiliximab or placebo.[18,20] The effect of basiliximab on ≥5-year graft and patient survival rates is not yet known.

- In contrast to those in the total population, graft survival rates in 2 high risk subpopulations of renal transplant recipients, diabetic and African-American patients, were significantly higher with basiliximab than placebo.[20,23] In a combined analysis of the US and European/Canadian trials, graft survival rates in diabetic patients were 96% with basiliximab and 86% with placebo ($p = 0.022$).[23] In African-American patients, graft survival rates were significantly higher with basiliximab than placebo at the 6-month time-point in the US trial (100 *vs* 92%, respectively, $p = 0.041$); the difference reached borderline significance at the 12-month time-point (98 *vs* 88%, $p = 0.059$).[20]

- Renal function after transplant was significantly better in patients who received basiliximab than in those who received placebo in the US trial, on the basis of the percentage of patients who produced urine in the operating theatre (94 *vs* 87%, respectively), incidence of delayed graft function (15 *vs* 23%) and mean creatinine clearance during the first 12 months after transplantation (except at the 12-week time-point).[20] In contrast, mean creatinine clearance was similar in patients who received basiliximab or placebo at all time-points in the European/Canadian trial.[18]

- The incidence of corticosteroid-resistant acute rejection episodes (requiring antibody therapy and/or azathioprine, tacrolimus or mycophenolate mofetil) was significantly lower in patients who received basiliximab than in placebo recipients 6 and 12 months after transplantation.[18,20] During the first 6 months after transplantation, 10% of patients who received basiliximab experienced corticosteroid-resistant first rejection episodes compared with 23% of placebo recipients in the European/Canadian trial ($p < 0.001$);[18] 24% of basiliximab versus 39% of placebo recipients experienced such episodes in the US trial ($p = 0.003$).[21]

- Median total direct medical costs per patient (including hospitalisations, outpatient visits, medical procedures, laboratory and diagnostic tests and medications other than basiliximab) were calculated to be significantly lower with basiliximab ($US26 479) than with placebo ($US32 241, $p = 0.03$) in the US trial; the difference was related to differences in the incidences of acute rejection, use of antibody therapy to treat rejection and hospitalisation for rejection.[24]

4. Tolerability

- Acute adverse events suggestive of hypersensitivity were not reported in patients who received basiliximab,[11,13,14,18,20] except for 1 patient who experienced transient facial flushing during an infusion in a noncomparative trial; the infusion was completed without further incident.[11] There were no reports of cytokine release syndrome (manifested as fever and chills and observed in most patients who receive muromonab CD3)[4] in comparative[18,20] and noncomparative[11,13,14] clinical trials of basiliximab.

- Infections (bacterial, viral, fungal and unspecified) occurred at similar rates in patients who received basiliximab or placebo; respective rates were 75 or 73% in the US and 85 or 86% in the European/Canadian trial.[18,20] Cytomegalovirus infections occurred with similar frequencies in basiliximab and placebo recipients; the respective incidences were 21 and 27% in the European/Canadian trial[18] and 7 and 9% in the US trial.[20]

- Post-transplant lymphoproliferative disorders[25] occurred in 0.3% (1 patient) of a total of 363

basiliximab recipients and 0.6% (2 patients) of 359 placebo recipients in the 12 months after transplant in the European/Canadian and US clinical trials; the Epstein-Barr virus status of patients was not reported.[15,18] In these 2 trials, a total of 13 patients (2%; 5 basiliximab and 8 placebo recipients) developed malignancies (adenocarcinoma, basal cell carcinoma, breast carcinoma, melanoma, cerebral glioma, hypernephroma, Kaposi's sarcoma, lymphoma, multiple myeloma and squamous cell carcinoma) in the first 12 months after transplant.[18,20]

- In clinical trials of basiliximab, vital signs or clinical laboratory test values did not differ significantly between basiliximab and placebo recipients at any time-point, with the exception of creatinine levels and clearance (see section 3).[18,20]

5. Basiliximab: Current Status

Basiliximab is a chimaeric mouse-human monoclonal antibody which inhibits T lymphocyte proliferation by antagonising IL-2 binding to its receptor. In combination with standard double immunosuppressive therapy, this drug has shown clinical efficacy in reducing the incidence of acute renal transplant rejection in 2 large, well-designed clinical trials. Basiliximab has been approved in the US and European Community, and is being investigated for prevention of rejection of liver transplants.[26-28]

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