REVIEW ARTICLE

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A Benefit-Risk Assessment of Basiliximab in Renal Transplantation

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Abstract

Interleukin-2 (IL-2) and its receptor (IL-2R) play a central role in T lymphocyte activation and immune response after transplantation. Research on the biology of IL-2R allowed the identification of key signal transduction pathways involved in the generation of proliferative and antiapoptotic signals in T cells. The α-chain of the IL-2R is a specific peptide against which monoclonal antibodies have been raised, with the aim of blunting the immune response by means of inhibiting proliferation and inducing apoptosis in primed lymphocytes. Indeed,

basiliximab, one of such antibodies, has proved to be effective in reducing the episodes of acute rejection after kidney and pancreas transplantation.

The use of basiliximab was associated with a significant reduction in the incidence of any treated rejection episodes after kidney transplantation in the two major randomised studies (placebo 52.2% vs basiliximab 34.2% at 6 months, European study; placebo 54.9% vs basiliximab 37.6% at 1 year, US trial). Basiliximab and equine antithymocyte globulin (ATG) administration resulted in a similar rate of biopsy-proven acute rejection at 6 months (19% for both) and at 12 months (19% and 20%, respectively). The use of basiliximab appears not to be associated with an increased incidence of adverse events as compared with placebo in immunosuppressive regimens, including calcineurin inhibitors, mycophenolate mofetil or azathioprine and corticosteroids, and its safety profile is superior to ATG. Moreover, a similar occurrence of infections is noted in selected studies (65.5% after basiliximab vs 65.7% of controls), including cytomegalovirus infection (17.3% vs 14.5%), and cytokine-release syndrome is not observed. Finally, economic analysis demonstrated lower costs of overall treatment in patients treated with basiliximab.

Therefore, the use of basiliximab entails a very low risk, allows safe reduction of corticosteroid dosage and reduces the short- and mid-term rejection rates. However, the improvement in the long-term survival of kidney grafts in patients treated according to modern immunosuppressive protocols is still to be demonstrated. These conclusions are based on a systematic review of the scientific literature, indexed on Medline database, concerning the mechanism of action, therapeutic activity, safety and pharmacoeconomic evaluation of basiliximab in renal transplantation.

With the exception of identical twins,[1] transplantation of a kidney to recipients with a fully reactive immune system is followed by rejection and eventually by graft loss, unless effective immunosuppression is provided.[2] A number of immunosuppressive drugs are currently available to prevent and/or reverse rejection episodes, with the ultimate aim of allowing the recipient's body to accept the allograft while retaining the ability to resist to infections and to control neoplastic growths. However, with current immunosuppressive regimens, acute rejection cannot be prevented in 30–50% of kidney recipients during the first year after transplantation, and transplant recipients may experience important drug-related adverse events.[3] The probability of acute rejection is higher for transplant recipients not yet under dialysis,[4,5] for younger individuals[6,7] and for African Americans.[6] Other relevant variables are the degree of human leucocyte antigen mismatch,[6] the level of panel reactive antibodies[3,8] and the occurrence of delayed graft function.[9] Therefore, according to host-specific factors, kidney recipients should be stratified into different risk categories in order to improve our understanding of the efficacy of each treatment protocol.

The purpose of this review is to evaluate the benefit-risk balance of basiliximab (Simulect®[1]) in kidney transplantation. Basiliximab is a chimeric monoclonal antibody directed against the α-chain (also known as CD25) of the interleukin-2 receptor

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

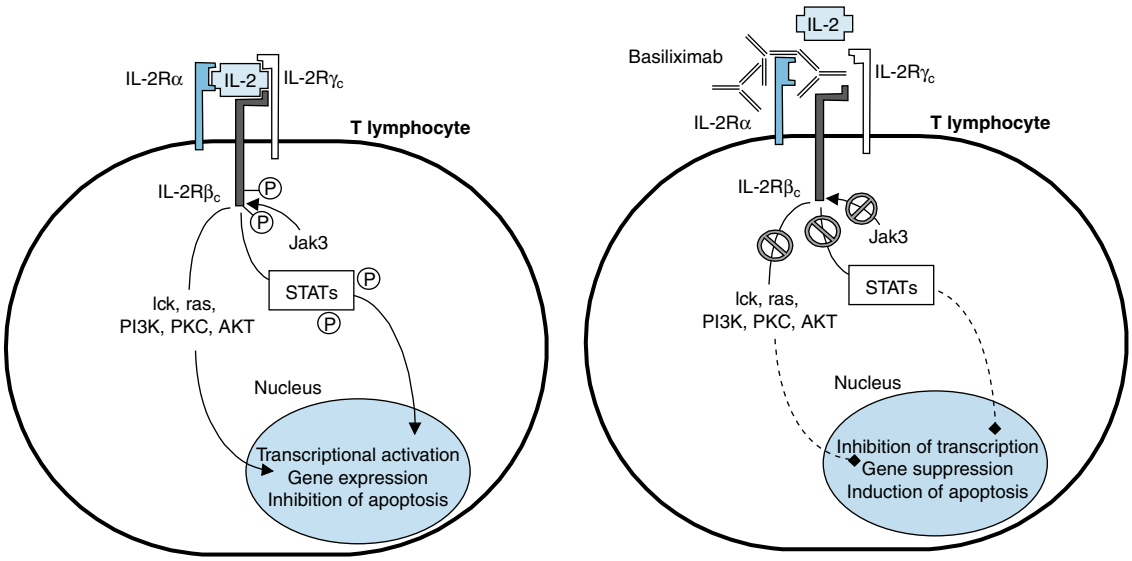

Fig. 1. Schematic representation of basiliximab and signal transduction events of IL-2/IL-2R. **AKT** = AKR mouse T-cell lymphoma kinase; **lck** = p56^{lck}; **IL-2** = interleukin; **IL-2R** = IL-2 receptor; **Jak3** = Janus kinase 3; **P** = phosphorylation of the substrate; **PI3K** = phosphatidylinositol 3-kinase; **PKC** = protein kinase C; **ras** = p21 ras protein; **STATs** = signal transduction and activators of transcription.

(IL-2R). It is registered in many countries, including the US and Europe, for use as an induction agent in association with different combinations of immunosuppressive drugs in the early post-transplant period.[10-22]

The review was carried out through the Internet-accessible MEDLINE database (http://www.ncbi.nlm.nih.gov/PubMed/) using multiple search terms and incorporating all pertinent papers published in English up to February 2003.

1. Mechanism of Action of Basiliximab

The activation of T lymphocytes is mediated by IL-2 upon binding to the cell surface receptor IL-2R, a heterotrimeric structure composed of a 55 kDa α-subunit (IL-2Rα), 75 kDa β_c-subunit (IL-2Rβ_c), and 39 kDa γ_c-subunit (IL-2Rγ_c) [figure 1]. The high-affinity binding of IL-2 is regulated by IL-2Rα, which is present only in IL-2R.[23] Although resting T cells express few IL-2Rα chains, IL-2R rapidly increases upon antigen challenge and graft rejection; furthermore, a 45 kDa soluble form of IL-2Rα (s-IL-2Rα) is released in the serum. Thus, s-IL-2Rα concentrations can be used to monitor T-cell activation.[23]

IL-2Rα is not involved in cell signalling because of its short intracellular domain. IL-2Rβ_c (CD122) and IL-2Rγ_c are both required for signal transduction, since they provide a link to intracellular effectors.[24] Most signalling pathways originate from IL-2R through phosphorylation of the cytoplasmic domain of IL-2Rβ_c on tyrosine residues.[24] Indeed, multiple tyrosine kinases are activated following IL-2R binding; as an example, the intracellular domain of IL-2Rγ_c is involved in the activation of p56^{lck}, which triggers anti-apoptotic mechanisms.[25] Moreover, tyrosine kinases, including Janus kinase 3 (Jak3), are activated in T cells challenged with an antigen, and contribute to the inhibition of apoptosis and promotion of cell proliferation.[25]

IL-2R and IL-15R of T cells possess the same IL-2Rβ_c and IL-2Rγ_c chains but the α-chains are receptor-specific.[25] Despite utilising the same receptor chains to transduce IL-2 signals, the two cytokines induce different cellular responses. Survival and antiapoptotic signals arising from IL-2R that lack the α-chains are mediated by the intracellular

domain of IL-2Rγ_c, and no activation of Jak3 occurs.[25] In contrast, when IL-2Rα is expressed, IL-2R signal transduction is associated with T-cell antigen receptor and Jak3 activation.[25]

The IL-2Rα-specific antibodies basiliximab (figure 1) and daclizumab are able to block IL-2-induced T-cell proliferation and induce apoptosis in antigen-primed T cells, thereby reducing the incidence of allograft rejection and also decreasing the severity of graft-versus-host disease after allogeneic bone marrow transplantation.[23]

In vitro studies demonstrated that after a short treatment with daclizumab, the viability of T cells was not affected and the expression of IL-2Rα-, IL-2Rβ_c- and IL-2Rγ_c-chains were unchanged.[26] Furthermore, daclizumab is able to inhibit ligand-induced association of IL-2R subunits, tyrosine phosphorylation of a cluster of 65-75 kDa proteins – most likely representing IL-2Rβ_c and IL-2Rγ_c – and to prevent the expression of the DNA-binding protein STAT5 (signal transduction and activator of transcription-5) after exposure of T cells to IL-2.[26]

If IL-2Rα-positive (CD25+) cells are treated with basiliximab, the proportion of IL-2Rβ_c-positive T cells decreases, and both IL-2- and IL-15-dependent proliferation is inhibited, as a consequence of downregulation of IL-2Rβ_c.[27] IL-2Rα saturation is obtained with basiliximab concentrations ≥0.2 μg/mL.[28] Immunosuppression with basiliximab, cyclosporin and mycophenolate mofetil (MMF) is associated with disappearance of CD25+ T cells for a median of 61 days in peripheral blood of patients.[27]

2. Pharmacokinetics and Drug Interactions of Basiliximab

A summary of main pharmacokinetic variables of basiliximab is given in table I.

Population models of basiliximab pharmacokinetics and pharmacodynamics were developed to optimise dosage regimens for IL-2Rα saturation after kidney transplantation.[33] Basiliximab disposition is characterised by a biphasic decline with long-terminal half-life, low clearance and small volume of distribution at steady state. This profile is consistent with distribution of the antibody in the blood and to some extent outside the plasma compartment, while its elimination from the body mainly results from slow intracellular proteolysis.

The pharmacokinetics of basiliximab are apparently not affected by bodyweight or gender.[28-30] Antibody clearance and the length of IL-2Rα saturation has no relationship with the occurrence or time of onset of acute rejection.[28,30,31,34]

Pharmacokinetic analysis has demonstrated that dosage modification is required for paediatric patients, such that patients weighing <35kg should receive basiliximab in two doses of 10mg, each while those weighing ≥35kg should be treated with two doses of 20mg.[32]

Basiliximab disposition may be significantly affected by concurrent immunosuppressive therapy, including a combination of cyclosporin microemulsion/corticosteroids, or cyclosporin microemulsion/corticosteroids/azathioprine or MMF. Furthermore, the administration of basiliximab significantly increased blood levels of cyclosporin in paediatric renal transplant recipients, and was associated with early drug toxicity compared with the control group.[35] As basiliximab concentrations declined, this was paralleled by a decline in cyclosporin concentrations, and higher doses of cyclosporin were required to maintain therapeutic trough levels.[35] These findings contrasted with additional studies[10,11,36] performed in paediatric and adult kidney transplant recipients, showing no apparent influence of basiliximab on cyclosporin disposition. However, evaluation of blood levels of tacrolimus in adult renal transplant recipients demonstrated that drug trough levels were higher in patients treated with basiliximab 20mg on day 0 and day 4 than in controls.[37] Tacrolimus trough levels on day 3 were ≥20 μg/L in 50% of patients administered basiliximab, compared with only a few patients not receiving basiliximab. Fifty percent of basiliximab-treated patients with elevated tacrolimus trough levels re-

Table I. Mean values of pharmacokinetic parameters of basiliximab in renal transplantation

Cumulative dose of basiliximab	Other treatments	Patients	$t_{1/2}$ (d)	C_{max} (μg/mL)	AUC (μg/mL • d)	CL (mL/h)	V_{SS} (L)	IL-2Rα saturation (d)	Reference
40mg[a]	CS, AZA (day 0) CSA (day 10)	24	6.5	9.3	41	46	8.9	26	29
60mg[a]	As above	6		11.6	72			32	
40mg[b]	μCSA, CS (day 0)	40	7.5	NR	NR	33	7.5	32 (rejection); 45 (no rejection)	30
40mg[b]	μCSA, CS (day 0)	169	7.4	NR	NR	36.7	8	36	28
40mg[b]	Dual (μCSA + CS)	111	7.4	NR	NR	36.7	8	36	31
	Dual + AZA	31	9.3*			29.3*	7.7	50*	
	Dual + MMF	66	11.5*			18.3*	6.2*	59*	
24 mg/m²[b]	μCSA, CS (day 0), AZA (day 28)	13	9.5 (<12y)	5.9	43	17	4.8	31	32
20/40mg[b,c]	As above	29	9.1 (12–16y)	5.7	59	31	7.8	36	

a Single dose on day 0.

b Two split doses on day 0 and day 4.

c Those weighing <40kg received 20mg, those weighing ≥40kg received 40mg.

AUC = area under the concentration-time curve; **AZA** = azathioprine; **CL** = clearance; **C_{max}** = maximum concentration; **CS** = corticosteroids; **CSA** = cyclosporin; **μCSA** = CSA microemulsion; **d** = day; **h** = hour; **IL-2Rα** = the α-chain of the interleukin-2 receptor; **MMF** = mycophenolate mofetil; **NR** = not reported; **$t_{1/2}$** = half-life; **V_{SS}** = volume of distribution at steady state; **y** = years of age of recipients; * $p < 0.05$.

Table II. Main results of European and US trials of basiliximab in combination with cyclosporin microemulsion/corticosteroids in renal transplantation

	European trial[10] 6 months' follow-up			US trial[11] 12 months' follow-up		
	placebo	basiliximab	p-value	placebo	basiliximab	p-value
Any treated rejection (%)	52.2	34.2	<0.001	54.9	37.6	0.001
First biopsy-proven rejection (%)	44.0	29.8	0.012	49.1	35.3	0.009
Second rejection episode (%)	8.6	7.9		23.9	11.6	0.005
Corticosteroid-resistant rejection treated with antibody therapy (%)	23.1	10.0	<0.001	29.9	20.2	0.034
Patient survival (%) [12 months]	97.3	95.3		96.0	97.1	
Graft survival (%) [12 months]	86.6	87.9		93.0	94.6	

quired at least two haemodialysis sessions during the first week post-transplant.[37]

Any interaction of basiliximab with cyclosporin and tacrolimus, both of which are substrates of cytochrome P450 (CYP) 3A4, may be mediated via cytokine-induced alterations in drug metabolism. Indeed, IL-2 may decrease the activity of CYP3A4 in intestinal epithelial cells and hepatocytes, and the increased availability of IL-2 following cytokine displacement by basiliximab may result in down-regulation of CYP3A4 activity.[35,37]

However, whether there is a significant pharmacokinetic interaction between basiliximab and substrates of CYP3A4 is still an open question, and there are no specific recommendations for therapeutic drug monitoring of cyclosporin and tacrolimus in patients receiving basiliximab.

3. Therapeutic Efficacy of Basiliximab in Renal Transplantation

3.1 Basiliximab in Combination with Cyclosporin Microemulsion/Corticosteroids

The efficacy of basiliximab in combination with cyclosporin microemulsion (Neoral®)/corticosteroids was assessed in two multicentre, randomised, double-blind, placebo-controlled phase III trials in patients undergoing renal transplantation.[10,11] Of the 728 transplant recipients enrolled in the two studies, 708 were eligible for the intention-to-treat analysis (356 basiliximab vs 352 placebo).

The main results of the European trial at 6 months and of the US trial at 12 months after transplantation are summarised in table II. Although the use of basiliximab was associated with a significant reduction in the incidence of acute rejection episodes, histopathological severity of rejection did not differ between basiliximab- and placebo-treated recipients. Similarly, despite reduction of early rejection episodes, 12-month graft survival rate was similar in the two treatment groups.[10,11] In both trials, placebo-treated recipients required significantly greater amounts of corticosteroids than basiliximab-treated recipients at week 2 (European trial: 1.42 vs 0.87 mg/kg/day, $p < 0.001$; US trial: 1.35 vs 0.89 mg/kg/day, $p = 0.004$) and at week 4 (European trial: 0.93 vs 0.56 mg/kg/day, $p < 0.001$; US trial: 0.78 vs 0.59 mg/kg/day, $p = 0.020$).[10,11]

In the US trial, a higher percentage of patients treated with basiliximab (94%) than with placebo (87%) produced urine in the operating room ($p = 0.030$). Accordingly, the incidence of delayed graft function was lower with basiliximab (15%) than with placebo (23%) [$p = 0.07$]. Basiliximab treatment significantly reduced rejection rates in male patients (58% vs 38%, $p = 0.002$), in patients <50 years of age (60% vs 38%, $p = 0.002$), in cadaveric

rather than living donor graft recipients (58% vs 42%, p = 0.012), and in patients who were not African Americans (53% vs 34%, p = 0.004). Notably, graft survival was better among African American patients treated with basiliximab than placebo at 6 months (100% vs 92%, p = 0.041), and at 12 months (98% vs 88%, p = 0.059). The composite index, resulting from the sum of adverse events such as graft loss, recipient death and rejection, was higher in placebo-treated (58.4%) than in basiliximab-treated recipients (41.0%, p = 0.001).[11]

3.2 Basiliximab in Combination with Cyclosporin Microemulsion/Azathioprine/Corticosteroids

The efficacy of basiliximab in combination with cyclosporin microemulsion/azathioprine/corticosteroids was assessed in a multicentre, randomised, double-blind, placebo-controlled trial in patients undergoing renal transplantation.[12] Of 345 transplant recipients enrolled in this study, 340 were eligible for the intention-to-treat analysis (172 placebo vs 168 basiliximab).

Assessed 6 months after transplantation, basiliximab significantly decreased the incidence of first acute rejection (20.8% vs 34.9%; p = 0.005) and biopsy-proven rejection episodes (18.5% vs 29.1%; p = 0.023), and the occurrence of multiple rejection episodes in the same patient (4.2% vs 7%; p = 0.026) compared with placebo. Serum creatinine levels were significantly lower in the basiliximab than in the placebo group 4 weeks after transplantation (160.3 vs 187.6 μmol/L; p = 0.026), but renal function was comparable in the groups after this point. The mean dose of corticosteroids was significantly lower with basiliximab as compared with placebo at 2 and 4 weeks after transplantation (p = 0.002).

However, basiliximab did not affect the severity of biopsy-proven rejections and failed to significantly reduce the rate of corticosteroid-resistant rejections necessitating antibody therapy (5.4% vs 9.9%; p = not significant [NS]), or necessitating antibody therapy, tacrolimus and MMF (9.5% vs 14%; p = NS) compared with placebo. At 12 months, the survival rates of graft (90.5% vs 88.4%; p = NS) and patients (97.6% vs 97.1%; p = NS) did not differ between basiliximab and placebo cohorts, although a significantly lower proportion of basiliximab-treated recipients experienced a treatment failure (acute rejection, graft loss or patient death) during the first 6 months after transplantation (25.6% vs 39.5%; p = 0.008).[12]

The efficacy of basiliximab was also evaluated in a recent prospective randomised trial comparing the following three treatment groups: cyclosporin microemulsion/azathioprine/corticosteroids (group 1; n = 25), cyclosporin microemulsion/MMF/corticosteroids (group 2; n = 23), and basiliximab/cyclosporin microemulsion/azathioprine/corticosteroids (group 3; n = 23).[13] The 6-month acute rejection rate was significantly reduced in group 3 (17.3%) in comparison with group 1 (32%; p = 0.05) but it was similar to rate of group 2 (21.7%). One-year graft survival rates were comparable among treatment groups and ranged from 88% in group 1 to 91.3% in groups 2 and 3.[13]

Finally, Boggi and coworkers[14] described the efficacy of basiliximab in combination with cyclosporin microemulsion/azathioprine or MMF/corticosteroids in a retrospective analysis of 286 cadaveric renal transplants with four different immunosuppressive regimens: basiliximab/cyclosporin microemulsion/MMF/corticosteroids (group 1; n = 78), basiliximab/cyclosporin microemulsion/azathioprine/corticosteroids (group 2; n = 33), cyclosporin microemulsion/MMF/corticosteroids (group 3; n = 64) and cyclosporin microemulsion/azathioprine/corticosteroids (group 4; n = 111). The acute rejection rate was reduced by basiliximab when the antibody was used in combination with azathioprine (group 2: 33.3% vs group 4: 59.4%; p = 0.008) but not with MMF (group 1: 15.3% vs group 3: 20.3%; p = NS). Early (3-month) patient and graft survival rates were not significantly influenced by the immunosuppressive regimen.[14]

3.3 Basiliximab in Combination with Cyclosporin Microemulsion/ Mycophenolate Mofetil/Corticosteroids

Basiliximab as induction therapy in combination with a regimen of cyclosporin microemulsion/ MMF/corticosteroids was compared with same regimen in combination with antithymocyte globulin (ATG) as induction therapy in two open-label, multicentre, randomised trials, and the efficacy was found to be similar.[15,16]

In the study reported by Sollinger and coworkers,[15] 70 transplant recipients were randomised to receive basiliximab and 68 to receive equine ATG. Basiliximab and ATG administration resulted in a similar rate of biopsy-proven acute rejection at 6 months (19% for both) and at 12 months (19% and 20%, respectively). The rate of any treated rejection at 6 and 12 months post-transplant was 30% and 31%, respectively, for the basiliximab group and 31% at both time-points for the ATG group. Acute rejection episodes requiring treatment with antibody therapy occurred in 11 patients in each treatment group. The incidence of biopsy-proven rejection, death or graft loss at 12 months was comparable in the two treatment groups, being 21.4% and 23.1%, respectively, for basiliximab and ATG. Kaplan-Meier estimates showed that the median time to first biopsy-proven acute rejection (62 vs 25 days, $p = 0.85$) and the time to first treated acute rejection (41 vs 17 days) were longer in patients treated with basiliximab than ATG, although the difference was not statistically significant. There were similar numbers of patients from each treatment arm with IA or IB rejection grades as assessed by the Banff classification of renal transplant pathology. No patient treated with basiliximab experienced a biopsy-confirmed acute rejection episode more severe than grade IIA. In contrast, one patient treated with ATG experienced grade IIB rejection and another patient experienced grade III rejection. Patient survival at 12 months was 66 of 70 (94%) for basiliximab and 63 of 65 (97%) for ATG; death-censored graft survival was 97% for basiliximab and 98% for ATG.[15]

Lebranchu and coworkers[16] reported a comparison between basiliximab and rabbit ATG. Of 103 eligible patients, 52 were randomised to basiliximab and 51 to rabbit ATG; 50 patients in each group were considered for the intention-to-treat analysis. The 6-month patient and graft survival rates were 98% and 94%, respectively, in the basiliximab group, compared with 100% and 100% in the ATG group. At month 12, patient and graft survival rates were unchanged in the basiliximab group, and were 100% and 96% in the ATG group, respectively. Acute rejection episodes requiring treatment occurred in four patients (8%) in the basiliximab group compared with six patients (12%) in the ATG group. However, two patients in the ATG group had rejection episodes that were not biopsy-confirmed, so that the rate of biopsy-confirmed rejection was identical (8%) in the two groups. All rejection episodes were either grade I or II. Seven patients (14%) in the basiliximab group had treatment failure (four acute rejections, two graft losses and one death), compared with four treatment failures (8%) in the ATG group, all of which were acute rejection (n = NS).[16]

3.4 Basiliximab in Diabetic Renal Transplant Recipients

Thistlethwaite and coworkers[17] reported on the efficacy of basiliximab in diabetic subgroups (including both type 1 and type 2 diabetes mellitus) from a *post hoc* analysis of the pooled results from two double-blind, multicentre, placebo-controlled phase III trials. Of a total of 150 diabetic renal transplant recipients eligible for the intention-to-treat analysis, 80 received basiliximab and 70 were treated with placebo.

When compared with placebo, basiliximab reduced the proportion of patients with first biopsy-confirmed rejection (−44%; $p < 0.01$), treated acute rejection (−41%; $p < 0.01$), acute rejection treated with antibody therapy, tacrolimus and MMF or azathioprine (−49%; $p < 0.01$), and acute rejection episode treated with antibody therapy (−47%; $p < 0.05$). Basiliximab also reduced the percentage of

patients with repeated rejection episodes (−67%; $p < 0.01$) and the cumulative rate of adverse events (death, graft loss or first rejection episode: −43%; $p < 0.001$). Accordingly, 1-year graft survival rates were improved by basiliximab in comparison with placebo (96% vs 86%; $p = 0.022$), although recipient survival rates were not affected (97% vs 94%).[17]

In an Italian experience, basiliximab was used in association with either cyclosporin microemulsion/MMF/corticosteroids or tacrolimus/MMF/corticosteroids in diabetic patients undergoing simultaneous pancreas-kidney transplantation. No acute pancreas rejection was recorded, while 33% of recipients experienced at least one kidney rejection episode. Three-month kidney graft survival rates were 93.7% and 100% with cyclosporin microemulsion and tacrolimus, respectively.[18]

3.5 Basiliximab in Transplant Recipients at High Risk of Rejection

In a prospective, controlled study of 148 renal transplants, the rates of acute rejection in patients treated with basiliximab were similar regardless of whether graft function was delayed (21%) or immediate (15%). Likewise, 1- and 2-year graft survival rates were not affected by delayed graft function (1 year: 88% vs 92%; 2 years: 86% vs 90%).[19]

3.6 Basiliximab in Paediatric Transplant Recipients

Basiliximab was used in a total of 128 paediatric kidney transplant recipients in three trials published between 2001 and 2002.[20-22]

Vester and coworkers[20] used basiliximab in 38 consecutive recipients in combination with cyclosporin microemulsion/ corticosteroids. The 1-year patient survival rate was 100% with an actuarial graft survival rate of 95%. Single rejection episodes were diagnosed in eight patients (21%) and two developed corticosteroid-resistant acute rejection.

Pape and coworkers[21] compared induction therapy with basiliximab (48 children) to a noninduction policy (29 children) in a prospective, nonrandomised trial using a maintenance regimen with cyclosporin microemulsion/corticosteroids. In the basiliximab group, a total of seven acute rejections (15%), of which two were corticosteroid resistant, were diagnosed between 3 and 14 weeks after transplantation. In contrast, ten children in the noninduction group experienced acute rejection episodes (34%; $p < 0.05$), including five corticosteroid-resistant episodes, over a wider time period of 7 days to 2 years after transplantation. At hospital discharge, 4–6 weeks after transplantation, glomerular filtration rate (GFR) was lower in the basiliximab group than in controls (51 ± 14 mL/min/1.73m^2 vs 66 ± 35 mL/min/1.73m^2; $p < 0.05$) but this difference gradually disappeared during the first year post-transplant (basiliximab 58 ± 21 mL/min/1.73m^2 vs control group 52 ± 19 mL/min/1.73m^2). Accordingly, 1-year graft survival rates were comparable between the two groups (basiliximab 95% vs controls 93%).[21]

Clark and coworkers[22] prospectively compared basiliximab plus cyclosporin microemulsion/corticosteroids with antilymphocyte globulin (ALG) plus cyclosporin microemulsion/azathioprine/corticosteroids. Forty-two children were enrolled in each study arm. No statistical difference in rejection rates was noted between treatment groups. Indeed, 55% of children receiving induction therapy with basiliximab experienced no rejection, 26% had one episode and 19% had two or more episodes (range 2–5). Equivalent figures for ALG-treated transplant recipients were 38%, 14% and 48% (range 2–9 episodes). Renal function at 6 months post-transplant was better in the basiliximab group than in the ALG group (GFR 69.1 ± 19 mL/min/1.73m^2 vs 58.2 ± 21 mL/min/1.73m^2; $p < 0.04$). However, correcting for the patient's body size, the absolute GFR 6 months after transplantation was not different (basiliximab 46 mL/min vs ALG 46.2 mL/min).

4. Safety Profile of Basiliximab

Several randomised studies examined the tolerability of intravenous basiliximab in renal transplantation.

A study of 722 renal transplant recipients (150 with diabetes, 572 without diabetes) treated with cyclosporin microemulsion/corticosteroids with or without basiliximab (20mg on day 0 and 20mg on day 4) demonstrated no significant differences in basiliximab tolerability in diabetic versus nondiabetic patients.[17]

The safety of a regimen of basiliximab 20mg on day 0 and on day 4 in addition to cyclosporin/corticosteroids/azathioprine was equivalent to the immunosuppressive regimen without basiliximab in a study of 340 patients.[12] Indeed, a similar occurrence of infections was noted (65.5% after basiliximab vs 65.7% of controls), including cytomegalovirus (CMV) infection (17.3% vs 14.5%), while malignancies occurred in three patients in the basiliximab group and in six controls during the first year post-transplant.[12] Furthermore, the mortality among 346 patients receiving maintenance immunosuppression with cyclosporin microemulsion/corticosteroids was 2.9% in those given basiliximab and 4% in controls; this finding reflects both the efficacy and tolerability of immunosuppression.[11] Urine output was improved immediately after transplant, and renal dysfunction (creatinine ≥5 mg/dL in the first month and ≥3 mg/dL at 1–12 months) occurred less frequently in patients given basiliximab than in the control group, providing evidence that antibody administration contributed to the efficacy of immunosuppressive treatment without harmful effects on the transplanted kidney. The occurrence of adverse events related to maintenance immunosuppression was unaffected by basiliximab (59% vs 61% of controls).[11]

The administration of basiliximab 20mg on day 0 and on day 4 or placebo in combination with cyclosporin/corticosteroids to 380 adult recipients of cadaveric kidney transplants was well tolerated. In particular, no cytokine-release syndrome (fever, hypertension, lung oedema or headache) was observed. Infection rates were similar in patients administered basiliximab compared with the placebo group (84.7% vs 86.6%), including urinary tract infections (58.4% vs 60.8%), and clinically evident CMV disease (20.5% vs 26.9%).[10] A similar incidence of malignancies, such as adenocarcinoma, melanoma, malignant glioma, Kaposi's sarcoma and lymphoproliferative disorders, were observed in the basiliximab and the placebo groups.[10]

In 138 adult renal transplant recipients treated with cyclosporin microemulsion/MMF/corticosteroids and basiliximab 20mg on day 0 and day 4 or ATG 15 mg/day intravenously for up to 14 days, the adverse events were more frequent during treatment with ATG (42%) than basiliximab (11%), while the incidence of malignancies, infections or death were unaffected by the choice of antibody.[15]

Basiliximab and daclizumab proved to have good safety profiles in a comparative study of 34 kidney-pancreas transplant recipients administered tacrolimus/MMF/corticosteroids with or without one of the anti-IL-2Rα antibodies. The event-free survival (absence of rejection episodes, graft loss, death or treatment-related complications) at 6 months was 59% in patients given induction immunosuppression with anti-IL-2Rα antibodies and 65% in the control group.[38] No significant differences in tacrolimus trough levels and daily dosages of tacrolimus, MMF and corticosteroids were observed between the two antibody groups compared with the control group after a 6-month follow-up; this finding suggests the absence of drug interactions, which further contributes to the safety of treatment. In this study two patients died because of sepsis and haemolytic uraemic syndrome.[38]

Nephrotoxicity and survival were examined in 77 children undergoing renal transplantation who were given immunosuppressive therapy with cyclosporin/prednisolone with or without basiliximab. A reduced GFR and higher cyclosporin trough levels (increasing the risk for nephrotoxicity) were observed in patients treated with basiliximab as compared

with the control group (GFR: 51 vs 66 mL/min/1.73 m^2; cyclosporin trough level: 214 vs 174 μg/L, respectively).[21] However, these differences disappeared after 1 year of follow-up, and no other adverse reactions were shown.[21]

The issue of safety of induction immunosuppression with basiliximab was also examined in non-randomised trials.

A study of 32 recipients of kidney grafts who were treated with basiliximab (40 or 60mg intravenously) plus cyclosporin/corticosteroids/azathioprine showed that treatment was well tolerated without cytokine-release syndrome or hypersensitivity reactions.[29]

A clinically significant difference was observed in the tolerability of basiliximab plus prednisolone/cyclosporin versus ATG plus prednisolone/cyclosporin/azathioprine in 84 children after renal transplantation.[22] One death due to food inhalation occurred in a patient treated with basiliximab, while another patient given ATG died because of *Pneumocystis carinii* pneumonia and lymphoproliferative disorder. CMV infection occurred in 10% of patients treated with basiliximab and dual drug therapy versus 19% of those receiving ATG and triple drug immunosuppression; none of the CMV-positive children had clinical infection after basiliximab, while almost half of the CMV-positive children who received ATG went on to develop CMV disease.[22] Furthermore, the incidences of infections, including CMV, and lymphoid malignancies in 38 children and 32 young patients who had undergone renal transplantation and were receiving immunosuppression with calcineurin inhibitors (cyclosporin or tacrolimus)/corticosteroids were not increased by the combination with basiliximab.[20,39]

Overall, intravenous basiliximab appears to have a good safety profile and to be well tolerated with a similar incidence of infections and malignancies as compared with patients not treated with basiliximab,[40-43] while anaphylactic reactions have been observed only rarely.[44]

5. Alternative Agents to Basiliximab for Induction Therapy

Traditionally, induction therapy is based on T-cell depleting agents such as muromonab CD3 (OKT3) or ATG. More recently, several new drugs, such as daclizumab, Campath-1 and FTY-720, have been developed with the same purpose.

5.1 Muromonab CD3 (OKT3)

OKT3 is a murine immunoglobulin G 2a (IgG_{2a}) monoclonal antibody that binds the ε-chain of the CD3 receptor, thus inducing immunological inactivation of T cells.[45] The effect is selectively exerted on CD3-expressing cells, the levels of which are markedly reduced within minutes after OKT3 administration.[3] OKT3 is used for both induction therapy and reversal of corticosteroid-resistant acute rejection.[3] As an induction agent, OKT3 reduces acute rejection rates, although it does not improve 1-year recipient and graft survival rates.[3] When it is used to rescue corticosteroid-resistant rejections, it reverses 80% of such episodes.[46]

Cytokine release syndrome, caused by T-cell activation, is very common following OKT3 administration and may cause a complex array of symptoms, including fever (73%), chills (57%), dyspnoea (21%), chest pain/tightness (14%), vomiting (13%), wheezing (11%), nausea (11%) and tremors (10%).[46] Moreover, local release of cytokines within the allograft may result in OKT3-induced nephropathy.[3] Nearly 50% of patients develop neutralising antimurine antibodies thus preventing further treatments after the initial course.[3] Finally, the administration of cumulative doses of OKT3 >75mg has been associated with the development of post-transplant lymphoproliferative disorders.[47]

5.2 Antithymocyte Globulin

ATG is a polyclonal antibody directed against human thymocytes. It is prepared from horses (ATGAM®) or rabbits (Thymoglobulin®). The antibody binds to a variety of lymphocyte surface antigens,

thus preparing the cell for digestion via complement-mediated lysis or reticulo-endothelial cell-dependent phagocytosis. When the T-lymphocyte count is reduced to 150 cells/mm^3 a profound immunosuppression is obtained.[3] Like OKT3, ATG may be used either as induction therapy or to reverse corticosteroid-resistant rejections. Rabbit ATG reverses more acute rejections (88%) than equine ATG (76%), even though 1-year patient (92.8% vs 96.3%) and graft (75% vs 83%) survival rates do not differ significantly.[48]

The major concerns regarding the routine use of ATG, especially in transplant recipients with a low immunological risk, lies in their potential to increase the rate of post-transplant lymphoproliferative disorders, although this issue has not been addressed exhaustively.

5.3 Daclizumab

Daclizumab is a humanised mouse anti-IL-2R monoclonal antibody directed against the IL2R α-chain (CD25).[48] Like basiliximab, daclizumab renders T lymphocytes unavailable for IL-2 binding, which is required for proliferation in response to this cytokine. Since daclizumab has a 10-fold lower avidity for CD25 than basiliximab, it is used at approximately 10-fold higher doses (1 mg/kg every other week starting before transplantation for a total of 5 doses).[3]

When daclizumab is added to cyclosporin/azathioprine/corticosteroids, it reduces the incidence of biopsy-proven acute rejections within the first 6 months (28% vs 43% for the placebo-treated controls).[49] No major adverse reactions were documented after daclizumab administration in comparison with placebo.[3]

5.4 Campath-1

Campath-1 is a rat antihuman IgG_{2b} monoclonal antibody that binds to CD52, a surface antigen common to B and T lymphocytes.[50] More recently, in order to prevent the formation of antibodies against the wild-type, cell-binding form and to permit multiple courses, a monomeric noncell-binding variant has been developed[51] and tested in humans.[52]

Following Campath-1 administration, the peripheral blood lymphocyte count falls to zero and recovers at about 1 month. The underlying principle is that the new lymphocytes should recognise as self the allograft antigens, thus promoting tolerance.[3] Campath-1 was tested in 31 renal transplant recipients in association with low-dose cyclosporin therapy.[53,54] The acute rejection rate was 16% and three grafts were lost because of recipient death (congestive hearth failure), recurrent kidney disease, and poor graft function, respectively. All recipients were maintained with a corticosteroid-free immunosuppressant regimen.

5.5 FTY-720

FTY-720 is a synthetic analogue of the sphingosine-like compound myriocin (ISP-1) produced by the ascomycete *Isaria sibclairii*.[3] FTY-720 markedly decreases the number of peripheral blood lymphocytes without affecting granulocyte and monocyte counts.[55] Moreover, FTY-720 acts synergistically with cyclosporin and rapamycin in rodent models[56] and shows an additive interaction with cyclosporin in primate transplant models.[57] In the first human study, FTY-720 caused a dose-dependent, rapidly reversible fall in peripheral blood lymphocyte count; however, bradycardia occurred in 10 of 32 transplant recipients.[58]

6. Pharmacoeconomics of Basiliximab

An analysis of the costs of hospitalisation, immunosuppressive drugs, treatment of graft rejection (including dialysis) and gain in survival in 380 adult renal transplant recipients demonstrated that basiliximab allowed an overall saving of $1554 Canadian dollars (1999 values) during the first year; patients received cyclosporin microemulsion/corticosteroids plus basiliximab 20mg intravenously on day 0 and on day 4 or placebo.[59] The savings were dependent on the reduced risks of acute rejection, graft dys-

Table III. Efficacy profile of basiliximab after a follow-up of 6 months (unless otherwise indicated) according to different protocols of immunosuppression

	A	B	C	p
Baseline therapy	CSA/CS[10]	CSA/AZA/CS[12]	CSA/MMF/CS[16]	
Patients eligible for the intention-to-treat analysis	190	168	50	
Any acute rejection episode	65 (34.2%)	35 (20.8%)	4 (8.0%)	A vs B, p = NS
				A vs C, p = 0.002
				B vs C, p = 0.04
First biopsy-proven rejection	51 (29.8%)[a]	31 (18.5%)	4 (8.0%)	A vs B, p = NS
				A vs C, p = 0.005
				B vs C, p = NS
≥2 Rejections	20 (10.5%)	7 (4.2%)	1 (2.0%)	A vs B, p = 0.02
				A vs C, p = NS
				B vs C, p = NS
Corticosteroid-resistant rejection treated with antibody therapy	19 (10.0%)	9 (5.4%)	0	A vs B, p < 0.0001
				A vs C, p = 0.0002
				B vs C, p = NS
Treatment failure[b]	NA	43 (25.6%)	7 (14%)	B vs C, p = NS
Graft survival (12 months)	87.9%	90.5%	94.0%	A vs B, p = NS
				A vs C, p = NS
				B vs C, p = NS
Patient survival (12 months)	95.3%	97.6%	98.0%	A vs B, p = NS
				A vs C, p = NS
				B vs C, p = NS

a 51/171 patients because one centre was excluded for non-compliance with the biopsy protocol.

b Treatment failure defined as first occurrence of acute rejection, graft loss, or death.

AZA = azathioprine; **CS** = corticosteroids; **CSA** = cyclosporin microemulsion; **MMF** = mycophenolate mofetil; **NA** = not available; **NS** = not significant.

function or loss, reduced need for dialysis and shorter hospital stay.[59]

Moreover, a study of 346 transplant recipients given cyclosporin microemulsion/corticosteroids with or without basiliximab demonstrated that the overall costs for the management of acute rejection during the first year were lower, albeit not significantly, with basiliximab versus placebo, while the incidence of acute rejections was significantly reduced from 55% (placebo) to 38% (basiliximab), and fewer patients required hospitalisation after basiliximab administration.[60] Furthermore, the incidence of infection was similar between groups and the costs of treatment-related adverse events were similar in patients treated with basiliximab or placebo.

Finally, the cost of induction immunosuppression with basiliximab ($US45 857) was significantly lower than ATG ($US54 729) [1997 values] in renal transplant recipients during the first year post-treatment, while quality-adjusted survival was similar in both groups.[61]

7. Conclusions

Modern immunosuppressive therapy allows increased graft survival with an acceptable tolerability profile. However, the impact of newer agents or drug combinations on survival and morbidity remains to be established. A number of important adverse events can occur with the drugs currently used in maintenance immunosuppressive regimens, including gingival hyperplasia, hirsutism, alopecia,

weight gain, hypertension, osteoporosis, nephrotoxicity, hyperlipidaemia and diabetes.[62] For this reason, reduction in the use of corticosteroids and calcineurin inhibitors in maintenance immunosuppression is warranted.[62]

The anti-IL-2Rα antibody basiliximab has proved to have a superior tolerability profile, particularly as compared with ATG, in the induction immunosuppression in kidney allograft recipients and in patients with diabetes. Safety appears to be the principal advantage associated with its use, thus providing a favourable benefit-to-risk ratio. This antibody is able to reduce the incidence of acute graft rejection episodes, although patients at high risk of rejection are best managed with ATG despite the higher toxicity burden. Furthermore, pharmacoeconomic analysis has provided evidence of reduced overall costs associated with basiliximab. Of note, reduction in acute rejection rates achieved with basiliximab was not associated with improved long-term graft survival rates. This phenomenon, already reported with other induction agents, such as OKT3,[3] may be at least in part explained by the enhanced efficacy of the newer agents used for maintenance immunosuppression. In particular, the use of MMF has been associated with a clear-cut decline in acute rejection rates after kidney transplantation (table III).

Thus, the use of basiliximab entails a very low risk and allows safe reduction of corticosteroid dosage but there is no final evidence that it improves the long-term survival of kidney graft in patients at low or very high risk of rejection when they are treated according to modern immunosuppressive protocols. Probably, the advantages of basiliximab induction are more evident in intermediate-risk kidney recipients, but no specific study has addressed this issue yet.

Finally, information concerning the long-term effects of basiliximab on malignancy, chronic rejection and survival are still sparse and additional data from clinical trials should be collected in order to define completely its role in immunosuppression.

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