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Safety and efficacy of an alternative basiliximab (Simulect) regimen after renal transplantation: administration of a single 40-mg dose on the first postoperative day in patients receiving triple therapy with azathioprine

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Abstract This was a multi-center, open-label, randomized, dose-comparative study on 202 renal transplantation patients. We evaluated for the first time an alternative dosing regimen for basiliximab, consisting of a single 40-mg intravenous dose on day 1 post-transplantation plus triple therapy, in comparison with the conventional two-dose regimen (2 h before transplantation and on day 4) plus triple therapy. At 6 months, the incidence of acute rejection was low: 22.5% of patients in the basiliximab 2×20-mg group and 20.0% of patients in the basiliximab 1×40-mg group experienced an acute rejection episode ($P=0.628$) (biopsy-proven rejection: 19.6% and 17.0%, $P=0.585$). There was no statistically significant difference in any of the secondary efficacy parameters. The incidence of graft loss by 12 months was 4.9% and 6.0% in the 2×20-mg and 1×40-mg group, respectively ($P=0.73$). No differences were observed between the dosage groups with regards to safety assessments (adverse events (AEs), infections, vital signs, laboratory safety evaluations, and physical examinations). The data reveal that basiliximab can be safely and effectively administered as a single 40-mg dose on day 1 after renal transplantation as a therapeutic option to the established 2×20-mg dosing regimen. This alternative dosing regimen may be of significant convenience under circumstances when a first dose of basiliximab was not given prior to transplantation. Both regimens can conveniently be used during the initial hospitalization of the patient.

Keywords Immunosuppression · Renal transplantation · Anti-IL-2 receptor · Basiliximab · Rejection · Simulect · Cyclosporin A

Introduction

The need for specific, less generally toxic immunosuppressive agents to prevent rejection after transplantation has been addressed by the development of monoclonal antibodies specific to the interleukin-2 (IL-2) receptor. The proliferation of activated T lymphocytes is a key step in the augmentation of an immune response, and is normally triggered when the cytokine IL-2 receptor is present on this cell type [1]. Basiliximab, a chimeric anti-CD25 antibody (Simulect, Novartis Pharma Basle, Switzerland), specifically binds to the 55-kD α-chain of the IL-2 receptor (also known as Tac antigen or CD25) with a high affinity. Basiliximab effectively competes with IL-2, and inhibits IL-2-driven proliferative responses to antigens and mitogens [1]. It was designed to

achieve high affinity and specificity for the IL-2 receptor subunit while reducing potential side effects and providing a convenient dosing regimen. The standard regimen for basiliximab as specified on the labeling is two 20-mg doses administered intravenously, with the first dose being administered 2 h prior to transplant surgery, and the second dose being given 4 days post-surgery [10]. Basiliximab dosing is not adjusted either to patient body weight or body surface area. This regimen ensures consistent suppression of the IL-2 receptor for 30 to 45 days [4, 5], during which time the risk of acute rejection is the highest.

Two large-scale randomized, controlled studies demonstrated the efficacy and safety of basiliximab in renal transplantation when added to the dual therapy with cyclosporin and steroids [3, 7]. Further studies demonstrated improved efficacy and comparable safety by adding basiliximab also to a triple therapy with cyclosporin A, azathioprine, and steroids in renal transplantation [8] and to a triple therapy with cyclosporin A, mycophenolate mofetil, and steroids in renal [2, 11] and kidney–pancreas transplantation, respectively.

In all these studies, the two-dose basiliximab regimen was followed closely. However, sometimes in clinical practice, special situations may arise which necessitate the use of an alternative dosing regimen (e.g., missed first dose; unexpected requirement of add-on immunosuppression emerging post-transplantation). An alternative dosing regimen of basiliximab may be appropriate for use under these circumstances.

The aim of this pilot study was to investigate an alternative regimen of basiliximab, whereby basiliximab would be administered as a single high-dose bolus on day 1 after renal transplantation, before background therapy with cyclosporin A (Neoral), steroids, and azathioprine. Results were compared with the standard two-dose regimen for basiliximab regarding efficacy, safety, and tolerability.

Material and methods

Ethics, institutional review board approval and informed consent

The study was conducted in full compliance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board at each participating institution, and written informed consent was obtained from each study patient.

Study population

Patients eligible for enrollment were male and female, undergoing their first mismatched cadaveric renal transplantation (up to, and including, 6 m/m HLA A, B, DR), aged 18–75 years and receiving cyclosporin A (Sandimmun Neoral), steroids and azathioprine. We excluded patients receiving a perfectly matched cadaveric kidney or a kidney from a living donor; patients undergoing their second or subsequent transplantation; multi-organ recipients; patients who had previously undergone transplantation; patients with a history of, or current, panel reactive T-cell antibodies of 80% or greater; patients with a severe, active infection. Also excluded were patients who had been treated with an investigational drug or investigational therapy within 1 month prior to entry, or who were liable to be treated in this manner within 12 months of undergoing transplantation; patients with positive serology for HIV or who were Hbe Ag positive for hepatitis B (Hbs Ag positive patients for whom Hbe Ag was negative could be included in the study); patients with a history of malignancy, except for excised squamous or basal cell carcinoma, within the past 5 years; patients with a history of alcohol or drug abuse or bearing signs of alcohol-induced organ damage, mental dysfunction or other factors limiting their ability to cooperate fully with the study.

Study design

This was a multi-center, open-label, randomized, controlled, parallel-group trial, which was conducted in six centers in the Czech Republic and in one center in Poland from September 1997 (first patient in) until April 2000 (last patient out).

To eliminate treatment bias, we randomized patients to two basiliximab dosage regimens in a 1:1 ratio: 2×20 mg vs. 1×40 mg, using code-breaker envelopes. Patients in the two-dose basiliximab group received the agent within 2 h prior to transplantation surgery at a dose of 20 mg as an intravenous (i.v.) bolus over 10 s; a second dose was administered as an i.v. bolus on day 4 after transplantation. Patients in the single-dose group received 40 mg basiliximab on day 1, i.e., after the transplantation operation.

All patients received maintenance triple-drug immunosuppressive therapy combining Sandimmun Neoral (Novartis Pharma Basle, Switzerland), steroids, and azathioprine for the first 12 months after transplantation. This background immunosuppressive regimen could be initiated before, during, or immediately after transplant surgery. The starting dose of Neoral was 10 mg/kg per day. Doses were adjusted to maintain cyclosporin trough whole-blood levels in the range of 300–400 ng/ml on days 1–6, 200–300 ng/ml on days 7–28, 150–250 ng/ml in months 2–6, and 100–200 ng/ml in months 6–12. Neoral doses were to be reduced where a diagnosis of drug-induced renal dysfunction was suggested by a clinical picture of either deteriorating renal function or where previously improving renal function reached a plateau with a serum creatinine above that judged to be clinically acceptable in an otherwise well patient. Steroids were commenced at a minimum dose of 30 mg/day, and then tapered according to the local practice in each center. However, a minimum dose of at least 10 mg/day was to be maintained for the duration of the whole study. Azathioprine was started at a dose of 1–2 mg/kg per day; it was to be reduced by 50% if the white blood cell count fell below 4×10^9/l, and be discontinued if it fell below 3×10^9/l.

Prophylactic medication

Patients received prophylactic medication according to local practice. This medication was to be commenced pre-operatively and continued throughout the initial 12-week study period. Co-trimoxazole, nifedipine, ranitidine, or cimetidine, and oral antifungal prophylaxis were recommended.

Patient assessment

The primary efficacy variable was the incidence of acute rejection episodes within 6 months following transplantation. Secondary endpoints included acute rejection until month 12, biopsy-proven rejection, graft loss, and death. Acute rejection was suspected whenever there was a rapid increase in plasma creatinine over the

previously stable baseline, not explained by complications other than rejection. The diagnosis of acute rejection was made whenever a patient had a positive biopsy, required anti-rejection therapy, and the investigator's final diagnosis confirmed the rejection episode. Patients with presumed acute renal rejection episodes underwent renal biopsy whenever possible before or within 24 h of the initiation of anti-rejection therapy. Biopsies were examined for evidence of rejection and graded according to severity by local pathologists using the Banff 1997 scale [9]. First acute rejection episodes were treated with steroids in accordance with local practice. If no decrease in serum creatinine was seen by days 4 or 5, a further biopsy was performed for the purpose of this study. If there was continuing evidence of rejection, patients could be treated with more-potent immunosuppressive agents (e.g., ATG, OKT3). In cases of vascular rejection, administration of antithymocyte globulins (ATG, OKT3) was allowed as first-line treatment.

Safety evaluation

Patient and graft survival, as well as clinical evaluation of laboratory variables, vital signs, graft function, and occurrence of adverse events (AEs) and serious adverse events (SAEs) were monitored regularly. In addition, graft function, severe infections, malignancies, and deaths were recorded at 6 and at 12 months.

Statistical analyses

All data were summarized for the prospective study population, comprising all patients who received (a) at least one dose of study medication (Simulect) and (b) the scheduled transplant. Kaplan-Meier survival analyses were performed for the time of the events (rejection, death, graft loss). Comparability of treatment regimens with regard to demographic and baseline characteristics were assessed either with Fisher's exact test for categorical variables or the Wilcoxon rank-sum test for continuous variables.

Confirmatory analyses of efficacy were based on a time interval of up to 6 months after transplantation. We performed comparisons between treatment regimens, using the Cochran-Mantel-Haenszel test adjusting for centers for the crude proportions of patients experiencing at least one episode of clinically confirmed and treated acute rejection and at least one episode of biopsy-proven and treated acute rejection. The proportions of patients with 0, 1, 2 or >2 acute rejection episodes were compared between treatment regimens for each of the above definitions of acute rejection, by the Cochran-Mantel-Haenszel test. Kaplan-Meie restimates and the log-rank test were used to compare the two treatment regimens for the time to each definition of acute rejection.

Secondary efficacy analyses were performed on the above-mentioned variables up to 12 months post-transplantation. In addition, acute rejections treated with antibody/tacrolimus/mycophenolate mofetil (MMF), patient survival, graft failure, and treatment failure, were analyzed up to 6 and 12 months post-transplantation, by Cochran-Mantel-Haenszel and Kaplan-Meier analyses.

Safety variables, AEs and laboratory data were assessed descriptively from summary statistics.

The sample size was derived from the practical recruitment rate of the centers and not based on statistical grounds.

Results

Demographic and baseline characteristics

There were 204 patients who entered the trial. Of these, one was not randomized because transplantation surgery was stopped after the donor was proved to be positive for *Staphylococcus aureus*. Another underwent transplantation but was not treated with basiliximab due to an administrative error. Therefore, there were 202 patients in the ITT population. At 12 months, 177 patients (87.6%) had completed the trial. Of the 25 patients (12.4%) who withdrew from the trial, 16 died, three withdrew consent, one experienced an AE, and three withdrew due to other reasons (Table 1).

Demographics and background characteristics were similar between groups (Table 2). The renal transplant population was predominantly male (65.3%), of Caucasian origin (100%), and had a mean age of 49.2 years. There were no major differences in the mean age or in the distribution of donor ages, in the recipient's past or

Table 1 Patient disposition for each treatment group

Parameter	Basiliximab 2×20 mg *n* (%)	Basiliximab 1×40 mg *n* (%)	Not randomized *n* (%)	Total patients *n* (%)
Total no. of patients				
Entered	102 (50.0)	101 (49.5)	1 (0.5)	204 (100.0)
Randomized	102 (50.2)	101 (49.8)		203 (100.0)
ITT[a]	102 (100.0)	100 (100.0)		202 (100.0)
Completed (month 12)[a]	88 (86.3)	89 (89.0)		177 (87.6)
Withdrawn (month 12)[a]	14 (13.7)	11 (11.0)		25 (12.4)
Discontinuations				
AEs[b]	1 (7.1)	0 (0.0)		1 (4.0)
Death[b]	8 (57.1)	8 (72.7)		16 (64.0)
Withdrawal of consent[b]	1 (7.1)	2 (18.2)		3 (12.0)
Protocol violation[b]	0 (0.0)	0 (0.0)		0 (0.0)
CRF treatment failure[b]	1 (7.1)	1 (9.1)		2 (8.0)
Failure to return[b]	0 (0.0)	0 (0.0)		0 (0.0)
Other[b]	3 (21.4)	0 (0.0)		3 (12.0)

[a]Denominator is number of ITT patients per treatment group
[b]Denominator is number of withdrawn ITT patients per treatment group

Table 2 Demographic and background characteristics at baseline, including history or renal disease, by treatment group

Demographic variable	Basiliximab 2×20 mg	Basiliximab 1×40 mg	Total
Gender *n* (%)			
Male	66 (64.7)	66 (66.0)	132 (65.3)
Female	36 (35.3)	34 (34.0)	70 (34.7)
Race *n* (%)			
Caucasian	102 (100.0)	100 (100.0)	202 (100.0)
Mean age (SD)	50.1 (11.11)	48.3 (11.01)	49.2 (11.07)
Cause of renal disease *n*(%)			
Glomerulonephritis	33 (32.4)	32 (32.0)	65 (32.2)
Polycystic kidney disease	17 (16.7)	13 (13.0)	30 (14.9)
Interstitial nephritis	27 (26.5)	31 (31.0)	58 (28.7)
Toxic nephropathy	0 (0)	1 (1.0)	1 (0.5)
Congenital	1 (1.0)	2 (2.0)	3 (1.5)
Vascular	6 (5.9)	5 (5.0)	11 (5.4)
Diabetic nephropathy	11 (10.8)	9 (9.0)	20 (9.9)
Other	7 (6.9)	7 (7.0	14 (6.9)
Total time on dialysis (months); mean (SD)	19.9 (21.3)	23.1 (21.7)	21.4 (21.5)
Number of mismatches at HLA locus; mean (SD)	3.2 (1.0)	2.9 (1.0)	3.1 (1.0)
Cold ischemia time (min); mean (SD)	1,093 (258)	1,100 (247)	1,097 (252)
Summary of donor age (years); mean (SD)	38.0 (15.6)	38.1 (13.8)	38.1 (14.7)

co-existing medical conditions, or regarding the causes of renal failure (data not shown).

All patients in the 1×40-mg Simulect group received the planned dose, whereas three of the 102 (2.9%) patients in the 2×20-mg Simulect group received only one 20-mg dose (patients withdrawn due to a positive cross-match, biopsy being contra-indicated, or an AE on day 4).

The mean daily doses of cyclosporin A at the start of the study were 7.9 mg/kg and 7.7 mg/kg. The recorded mean trough levels in these patients were 301 and 265 ng/ml in the 2×20-mg and 1×40-mg basiliximab group, respectively. By day 10, mean trough levels in both treatment groups increased to 330 and 319 ng/ml, respectively. At month 12, they measured 163 and 171 ng/ml for each respective treatment group. Similarly, steroid treatment as well as azathioprine treatment was well balanced between groups (e.g., the mean prednisone equivalent on day 0 was 5.7 and 5.6 mg/kg per day).

Just over one-third of all study patients, 38/102 and 34/100 in the 2×20-mg and 1×40-mg basiliximab treatment groups, respectively, underwent other immunosuppressive therapies during the course of the study. The majority received intravenous cyclosporin (23 patients in each treatment group; stopped in all cases by day 2). Excluding intravenous cyclosporin, 15 (14.7%) and 14 (14.0%) patients in the 2×20-mg and 1×40-mg basiliximab groups received ALG/ATG, OKT3, MMF or tacrolimus.

Efficacy

No differences were observed between the treatment groups regarding the primary efficacy endpoint and the secondary efficacy endpoints during the 6 months post-transplantation (Table 3). In both groups, the incidence of acute rejections was low (22.5% in the basiliximab 2×20-mg group, 20.0% in the 1×40-mg group, $P=0.628$). Similarly, the treatment groups were comparable with regards to the number of biopsy-proven acute rejection episodes (19.6% of patients in the basiliximab 2×20-mg group and 17.0% in the basiliximab 1×40-mg group, $P=0.585$). The number of steroid-resistant acute rejections requiring antibody, tacrolimus or MMF treatment was somewhat higher in the basiliximab 1×40-mg group (7.0%) than in the 2×20-mg group (3.9%, $P=0.341$). Likewise, the incidence of death or graft loss was higher in the 1×40-mg group than in the control group. However, the differences did not reach statistical significance.

These results for the parameters described above were very similar for the month-12 outcomes. From month 6 until the end of month 12, only two additional patients, both in the basiliximab 2×20-mg group, experienced a first acute rejection. None of the secondary outcomes was statistically significantly different at month 12 between the treatment groups (Table 3).

The time to the first acute rejection episode, with respect to day 0, as analyzed by the Kaplan-Meier estimator, is shown in Fig. 1. In terms of formal comparisons, there was no evidence for a statistically significant difference between the treatment groups (at 6 months: log-rank P value = 0.593, Wilcoxon P value = 0.562).

There was no difference between the treatment groups regarding the composite index of treatment failure consisting of acute rejection episode, death, or graft loss, whichever occurred first. Twenty-eight patients (27.5%) in the basiliximab 2×20-mg group, and 29 patients (29.0%) in the basiliximab 1×40-mg group experienced

Table 3 Summary of incidence of efficacy variables during the 6-month and 12-month post-transplantation. Percentages are based on the number of ITT population patients in each treatment group periods; *P* values were calculated by Cochran-Mantel-Haenszel general association test adjusting for centers

Variable	Basiliximab 2×20 mg ($n=102$) *n* (%)	Basiliximab 1×40 mg ($n=100$) *n* (%)	All patients ($n=202$) *n* (%)	*P*
Months 1–6				
First acute rejection episode[d]	23 (22.5)	20 (20.0)	43 (21.3)	0.628
Biopsy-proven rejection episode[a]	20 (19.6)	17 (17.0)	37 (18.3)	0.585
Acute rejection treated with antibody therapy, tacrolimus or MMF[b]	4 (3.9)	7 (7.0)	11 (5.4)	0.341
Death	3 (2.9)	6 (6.0)	9 (4.5)	0.252
Graft loss	5 (4.9)	5 (5.0)	10 (5.0)	0.98
Death or graft loss[c]	7 (6.9)	11 (11.0)	18 (8.9)	0.291
Months 1–12				
First acute rejection episode[d]	25 (24.5)	20 (20.0)	45 (22.3)	0.417
Biopsy-proven rejection episode[a]	22 (21.6)	18 (18.0)	40 (19.8)	0.492
Acute rejection treated with antibody therapy, tacrolimus or MMF[b]	5 (4.9)	9 (9.0)	14 (9.6)	0.233
Death	9 (8.8)	8 (8.0)	17 (8.4)	0.873
Graft loss	5 (4.9)	6 (6.0)	11 (5.4)	0.73
Death or graft loss[c]	12 (11.8)	14 (14.0)	26 (12.9)	0.618

[a]Defined as an acute rejection episode which has been confirmed by biopsy
[b]Patient may be included in both categories for treatment rejection
[c]Death or graft loss, whichever occurs first
[d]Defined as the first rejection episode which is (1) confirmed by the investigator and (2) treated with anti-rejection therapy

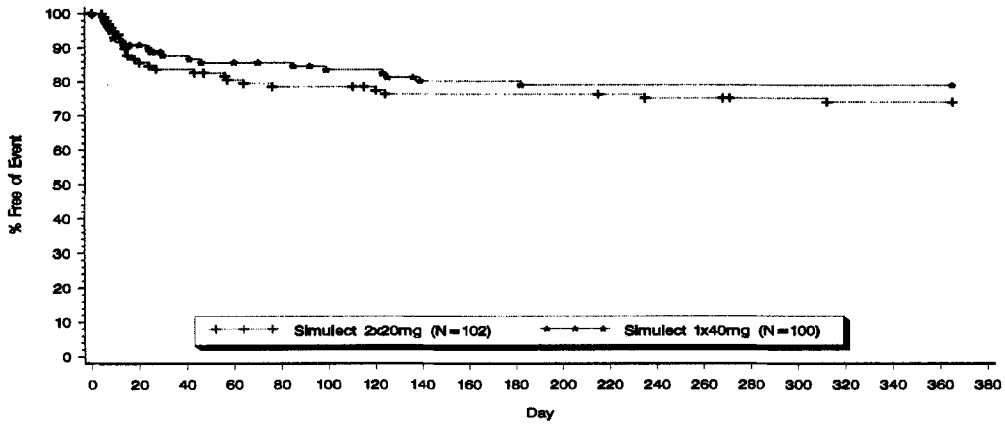

Fig. 1 Time to first acute rejection episode with respect to day 0 (ITT population)

treatment failure during the first 6 months after transplantation ($P=0.796$). The corresponding rates during the 12-month period were 33 (32.4%) and 30 (30.0%) ($P=0.720$). The causes for graft loss are summarized in Table 4.

Renal function was monitored by measurement of serum creatinine levels. A rapid decline in serum creatinine levels was observed for both treatment groups within the first week post-transplantation (Fig. 2). Steady serum creatinine levels of comparable value for both groups were reached at around day 14 after transplantation and remained at stable levels throughout the 12-month observation period. Median serum creatinine levels at month 12 were 129.1 μmol/l and 128.6 μmol/l for the 2×20-mg and 1×40-mg group, respectively.

Safety

The safety profiles of the two basiliximab regimens did not differ, as assessed by AE and SAE, infections vital sign, laboratory safety assessment, and physical assessment.

The majority of patients (79.2%) reported at least one AE during the study, as would be expected in an immunosuppressed post-transplantation patient population. In total, 12.4% of patients reported AEs with at least a possible causal relationship with the study medication (14.7% in the basiliximab 2×20-mg group and 10.0% in the basiliximab 1×40 mg group). Only one AE led to study discontinuation; one patient in the basiliximab 2×20-mg group was withdrawn from the study on day 4 due to thrombosis of the renal artery, necessitating graft nephrectomy (event rated as not study-drug related) and

Table 4 Causes of graft loss

Primary cause of graft loss	Basiliximab 2×20 mg ($n=102$) n (%)	Basiliximab 1×40 mg ($n=100$) n (%)	All patients ($n=202$) n (%)
Any graft loss	5 (4.9)	6 (6.0)	11 (5.4)
Acute rejection	0 (0.0)	1 (1.0)	1 (0.5)
Chronic rejection	1 (1.0)	0 (0.0)	1 (0.5)
Primary non-function	2 (2.0)	2 (2.0)	4 (2.0)
Infarcted kidney	1 (1.0)	0 (0.0)	1 (0.5)
Technical – other	1 (1.0)	0 (0.0)	1 (0.5)
Technical – renal vein thrombosis	0 (0.0)	2 (2.0)	2 (1.0)
Urological complications	0 (0.0)	1 (1.0)	1 (0.5)

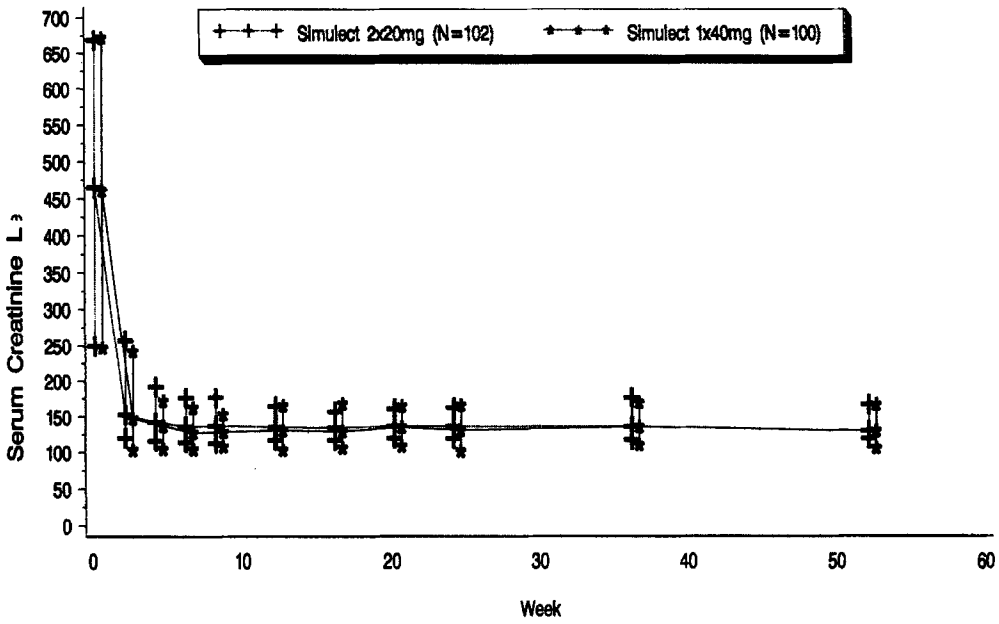

Fig. 2 Serum creatinine levels (median and interquartile range) in the ITT population

did not receive the second dose of basiliximab. Of the AEs reported on the days of study-drug administration, only three were assessed as possibly related to the study medication: elevation of hepatic enzymes, hepatocellular damage, and nausea. In total, 26.7% of patients experienced SAEs (27.5% in the basiliximab 2×20-mg group and 26.0% in the basiliximab 1×40-mg group; for details see Table 5). No local-injection-site reactions were reported. Additionally, there was no evidence of cytokine-release syndrome or anaphylaxis.

Given the immunosuppressed status of the patient population, the high incidence of infections was not surprising and was consistent with the incidence rates observed in prior clinical studies. The overall incidence of infection was very similar for both treatment groups; 76.5% of patients in the basiliximab 2×20-mg group and 75.0% in the 1×40-mg group reported infections during the study period. Serious infections during the study period were reported in 13 (12.7%) in the 2×20-mg group, and in 14 cases (14.0%) in the 1×40-mggroup, of which four and three, respectively, were CMV infections.

During the 12-month study period, there were 17 deaths: nine in the basiliximab 2×20-mg group, and eight in the 1×40-mg group. Only one death was assessed as causally related to the study medication. The patient in the basiliximab 1×40-mg group died from bronchopneumonia. This event was assessed by the investigator, in the corresponding SAE report, as being possibly related to the study medication.

No post-transplantation lymphoproliferative disorders were reported during the study period. One patient in the basiliximab 1×40-mg group was diagnosed on day 21 as suffering from an adenocarcinoma with tumor metastases in the liver and local lymph nodes. The investigator assessed that the neoplasm as not causally related to the study medication.

Discussion

The main conclusions that may be drawn from the present study were (a) that the use of an alternative, single-dose 40-mg basiliximab regimen did not differ

Table 5 Number (%) of patients with SAEs by body system and most frequent SAEs (>2% patients affected in either group) by preferred term

Parameter	Basiliximab 2×20 mg ($n=102$)	Basiliximab 1×40 mg ($n=100$)	All patients ($n=202$)
Total number of SAEs	36	38	74
Number of patients with SAEs	28 (27.5)	26 (26.0)	54 (26.7)
Body systems affected and the most frequent SAE (>2% patients affected in either group) by preferred term			
Cardiovascular disorders, general	4 (3.9)	3 (3.0)	7 (3.5)
Central and peripheral nervous system disorders	1 (1.0)	1 (1.0)	2 (1.0)
Gastrointestinal system disorders	2 (2.0)	5 (5.0)	7 (3.5)
Pancreatitis	1 (1.0)	3 (3.0)	4 (2.0)
Metabolic and nutritional disorders	3 (2.9)	0 (0.0)	3 (1.5)
Diabetes mellitus	3 (2.9)	0 (0.0)	3 (1.5)
Myo-, endo-, pericardial and valve disorders	2 (2.0)	3 (3.0)	5 (2.5)
Red blood cell disorders	1 (1.0)	0 (0.0)	1 (0.5)
Skin and appendage disorders	2 (2.0)	1 (1.0)	3 (1.5)
Urinary system disorders	6 (5.9)	6 (6.0)	12 (5.9)
Nephropathy toxic	2 (2.0)	3 (3.0)	5 (2.5)
Vascular (extra-cardiac) disorders	10 (9.8)	8 (8.0)	18 (8.9)
Cerebrovascular disorder	3 (2.9)	1 (1.0)	4 (2.0)
White cell and reticuloendothelial system disorders	2 (2.0)	0 (0.0)	2 (1.0)
Body as a whole – general disorders	0 (0.0)	2 (2.0)	2 (1.0)
Musculo-skeletal system disorders	0 (0.0)	3 (3.0)	3 (1.5)
Neoplasms	0 (0.0)	1 (1.0)	1 (0.5)

from the standard two-dose regimen in terms of efficacy, safety, and tolerability, and (b) the results are generally in line with those observed in other trials investigating basiliximab with triple immunosuppressive therapy.

Two placebo-controlled phase-III de-novo renal transplant studies (CHIB 201 and CHIB 352) investigating the efficacy and safety of basiliximab have shown that the 40-mg dose of basiliximab given peri-operatively (i.e., within the first week of transplantation) was the dose that consistently suppressed the IL-2 receptor (IL-2R) for 30–45 days post-transplant [3, 7]. The chosen dose of basiliximab in adult renal transplantation is a 40-mg cumulative dose, 20 mg being given intravenously on day 0 within 2 h prior to transplant surgery, and 20 mg on day 4 post-transplantation. This cumulative dose is able to block IL-2Rα for an average 4–6 weeks post-transplantation without a pronounced risk of prolonged immunosuppression beyond 6 weeks. Administration of two 20-mg doses were chosen, based on practical clinical considerations. This mode of administration would allow the second dose to be withheld if the transplant operation did not proceed or if complications (graft loss, severe infection, etc.) arose in the immediate post-transplant days. An interval of 4 days was defined because it maintained a serum concentration above the saturation threshold while minimizing the potential for "suppression breakthrough" due to low concentrations of the second dose [4].

In special situations, deviations from the described regimen may occur. For example, in patients experiencing acute tubular necrosis, with the resulting necessity of having their cyclosporin levels reduced, additional immunosuppression covering the first days or weeks is useful and may consist of basiliximab. In other cases, the first dose of basiliximab might have been planned but erroneously missed pre-operatively. The present study shows that a "delayed" start of basiliximab therapy is efficacious and safe, if the 40-mg total dose is maintained. Since the protocol allowed a certain degree of flexibility in the choice of immunosuppression, these results apply to a variety of clinical situations, e.g., when intravenous cyclosporin instead of Neoral is used during the first days.

The study suggests that there are no important differences between either basiliximab regimen in terms of efficacy and safety. Concerning the incidence of first acute rejections up to 6 months after transplantation, the levels reported in this study for basiliximab 2×20 mg and 1×40 mg (22.5% and 20.0%; biopsy proven: 19.6% and 17.0%) are in line with the 20.8% (biopsy proven: 18.5%) reported in a recent study of basiliximab 2×20 mg in renal transplant patients receiving the same triple immunosuppressive background regimen [8]. These trials indicate that basiliximab provides improved efficacy when added to either a dual or triple therapy regimen. A lower incidence of acute rejection in combination with triple therapy compared with dual therapy has been reported in several clinical trials: In the American and the European basiliximab dual therapy studies, patients experienced biopsy-proven rejection episodes in 35.3% (placebo: 49.1%, P between groups = 0.009) and 29.8% (placebo: 44.0%; $P=0.012$) [3, 7]. A reason for this finding might be that both azathioprine and MMF decrease the clearance of basiliximab from the circulation, which leads to an increased duration of CD25 saturation compared with dual therapy [6].

In terms of safety, no differences were observed between the dosage groups regarding safety assessments at

month 12 (AEs, infections, vital signs, laboratory safety evaluations, and physical examinations). The numbers of AEs reported on the days of study-drug administration were comparable to those reported on the same day in the opposite-treatment group. Only one neoplasm occurred. No case of cytokine-release syndrome was observed, nor of leucopenia or thrombocytopenia, or PTLD. Notably, too, there was no increase in the incidence of CMV infections, which supports the finding that basiliximab is a highly effective immunosuppressant without the diminution of an effective immune response that is associated with over-immunosuppression.

The strong overall similarity of results between the two basiliximab regimens is likely due to the long-lasting therapeutic effect of basiliximab (approximately 4 to 6 weeks). Provision of the optimal total dose of 40 mg above the immunosuppression threshold seems to be the decisive factor for a positive outcome, rather than strict adherence to a day-0 to day-4 dosing regimen. From a clinical perspective, these results are of great practical importance because they demonstrate that if the decision to use basiliximab is not made on the day of transplantation, it can still be made on the first post-operative day without any clinical drawbacks.

In conclusion, the combination of basiliximab with maintenance immunosuppressive triple therapy (Sandimmun Neoral, steroids and azathioprine) has been confirmed to be an effective treatment regimen regarding prophylaxis of acute rejection and tolerability. As an additional option to the established two-dose regimen, basiliximab can safely and effectively be administered as a single 40-mg dose bolus injection on day 1 after renal transplantation. In both regimens, basiliximab can conveniently be administered during the initial hospitalization of the patient.

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