

ANAPHYLACTIC SHOCK CAUSED BY IMMUNOGLOBULIN E SENSITIZATION AFTER RETREATMENT WITH THE CHIMERIC ANTI-INTERLEUKIN-2 RECEPTOR MONOCLONAL ANTIBODY BASILIXIMAB

VÉRONIQUE BAUDOUIN,¹ ALAIN CRUSIAUX,² ELIE HADDAD,¹ LILIANE SCHANDENE,² MICHEL GOLDMAN,² CHANTAL LOIRAT,¹ AND DANIEL ABRAMOWICZ^{3,4}

Background. Repeated administration of chimeric or humanized monoclonal antibodies is generally well tolerated. Anti-idiotypic sensitization is rare and is considered to be of no clinical significance. We observed a child who experienced anaphylactic shock when he received a second course of basiliximab at the time of his second renal transplantation. We therefore searched for the presence of anti-basiliximab immunoglobulin (Ig) E in this patient.

Methods. Serum levels of anti-basiliximab IgE, assay of the anti-murine reactivity of circulating anti-basiliximab IgE, and assays for serum anti-mouse antibodies and global anti-basiliximab anti-idiotypic antibodies were carried out by enzyme-linked immunosorbent assay. Anti-basiliximab IgE antibodies on circulating basophils were evaluated by the ability of the patient's blood to produce leukotrienes *in vitro* after exposure to basiliximab.

Results. Sequential assays of serum samples by enzyme-linked immunosorbent assay indicated that anti-basiliximab IgE antibodies appeared after the second basiliximab course. There was no IgE reactivity toward a control murine IgG2a monoclonal antibody (mAb), indicating that the IgE response was directed exclusively against basiliximab idiotypes. There was no IgE reactivity against the humanized anti-interleukin-2 receptor mAb daclizumab, which was derived from a distinct parental murine mAb. Patient basophils harvested months after the anaphylactic shock produced leukotrienes *in vitro* on exposure to basiliximab.

Conclusions. Patients exposed to chimeric antibodies may develop an anti-idiotypic IgE response that can trigger anaphylactic shock on further exposure. Specific anti-idiotypic IgE may be bound to basophils even in the absence of circulating IgE.

Basiliximab (Simulect, Novartis Pharma AG, Basel, Switzerland) and daclizumab (Zenapax, Hoffmann-LaRoche Pharma, Nutley, NJ) are monoclonal antibodies (mAb) directed against the α -chain of the high affinity interleukin (IL)-2 receptor (R) complex (CD25). Both antibodies reduce rejection rates by approximately 30% in kidney transplant recipients when added to cyclosporine A (CsA)-based immunosuppressive regimens (1–6). Basiliximab and daclizumab are derived from two distinct

parental mouse mAb, RFT5 γ 2a and anti-Tac, respectively. Basiliximab was constructed by grafting the entire Fab variable regions of the parental mouse antibody on the constant regions of a human immunoglobulin (Ig) G1 molecule and is therefore a chimeric antibody (7). Daclizumab is a humanized IgG1 mAb, as it retains from its murine anti-Tac parent only the mouse hypervariable antigen-binding sequences (8). Although anti-idiotypic sensitization may still occur, the overall antigenic load of chimeric and humanized antibodies is considerably less as compared with rodent antibodies. This is reflected by sensitization rates below 2% among patients who were treated with basiliximab or daclizumab (2, 9). Nevertheless, postmarketing surveillance revealed that 17 cases of hypersensitivity reactions, including anaphylaxis, did occur after exposure or reexposure to basiliximab. In this article, we report a case of anaphylactic shock that developed after a second course of basiliximab. In addition, we characterized the anti-basiliximab antibody response and investigated whether the sensitization process was cross-reactive with daclizumab.

CASE REPORTS

A 3-year-old boy had been on cyclic peritoneal dialysis since the age of 7 months because of end-stage renal failure caused by bilateral renal hypoplasia. At age 2 years, he had received a first renal transplant from his mother. Immunosuppression consisted of basiliximab (10 mg) together with CsA and prednisone. Arterial thrombosis of technical origin occurred immediately. The graft was removed and immunosuppressive therapy was stopped on day 2. Thus, the patient had received only one injection of basiliximab. Nine months later, he received a cadaveric kidney. Immunosuppression consisted again of basiliximab, CsA, and prednisone. The basiliximab injection was initiated during the surgical procedure. A few minutes later, blood pressure suddenly dropped and severe bronchospasm occurred. Basiliximab infusion was stopped immediately; only 5 mg had been given. Blood pressure remained below 20 mm Hg despite massive intravenous fluid therapy, and continuous intravenous adrenaline infusion had to be started. After 45 min of blood pressure collapse, normal hemodynamic status could be restored and surgery was completed. Graft function was immediate. Serum creatinine was 40 μ M at day 2 and remains so to date after 15 months' follow-up under CsA, prednisone, and mycophenolate mofetil immunosuppressive therapy.

MATERIALS AND METHODS

Anti-basiliximab IgE Antibodies in Serum

Enzyme-linked immunosorbent assay (ELISA) plates were coated with a rabbit anti-human IgE reagent (1 μ g/well) (ref. A0094, DAKO,

¹ Department of Nephrology, Hopital Robert Debré, Paris, France.

² Department of Immunology, Hopital Erasme, Brussels, Belgium.

³ Department of Nephrology, Hopital Erasme, Brussels, Belgium.

⁴ Address correspondence to: Daniel Abramowicz, M.D., Ph.D., Department of Nephrology, Hôpital Erasme, 808 route de Lennik, 1070 Brussels, Belgium. E-mail: dabram@ulb.ac.be.

Received 18 November 2002. Revised 23 December 2002. Accepted 26 March 2003.

DOI: 10.1097/01.TP.0000073809.65502.8F

Denmark) to capture circulating IgE on the plates. A 1:10 dilution of serum was added in duplicate for 2 hr at room temperature, allowing for the binding of serum IgE. The plates were then incubated with biotinylated basiliximab or daclizumab (0.5 μ g/well). Bound antibodies were revealed by the sequential addition of streptavidin-peroxidase and tetramethylbenzidine. Results were expressed as optical density.

Assays for Anti-murine Reactivity of Circulating Anti-basiliximab IgE

This was evaluated by two methods. First, we performed a binding inhibition assay using the ELISA described above. After IgE binding, plates were incubated for 2 hr at room temperature with a purified unlabeled third-party murine IgG2a mAb to which the patient had never been exposed (OKT3, 0.5 μ g/well). This amount of IgG2a mAb was previously defined to be optimal in similar blocking experiments (10). We then added biotinylated basiliximab, streptavidin-peroxidase, and tetramethylbenzidine as described above. The same test was performed without the addition of the murine IgG2a mAb. Inhibition of binding of biotinylated basiliximab by the murine IgG2a mAb indicates IgE reactivity to murine IgG2a epitopes. Results were expressed as optical density. In a second assay, we directly evaluated the ability of patient IgE to bind the third-party murine IgG2a mAb OKT3. After IgE binding on ELISA plates as described above, incubation was performed for 2 hr at room temperature with either biotinylated basiliximab or biotinylated OKT3 (0.1 μ g/well). Bounded biotinylated antibodies were revealed as above. Results were expressed as optical density. As a positive control for IgE reactivity against the OKT3 murine IgG2a mAb, we tested a serum known to contain anti-OKT3 IgE antibodies (10).

Anti-basiliximab IgE Antibodies on Circulating Basophils

This was searched by a commercially available ELISA assay (CAST-2000 ELISA; Bühlmann Laboratories, Allschwil, Switzerland). Briefly, leukocytes isolated from heparinized blood by dextran sedimentation were incubated with basiliximab and daclizumab, and with an anti-IgE mAb as positive control. After 40 min, leukotriene (LT) C4, LTD4, and LTE4 were quantified by ELISA on the basis of reactivity with a specific anti-LT mAb.

Assays for Serum Anti-mouse Antibodies and Global Anti-basiliximab Anti-idiotypic Antibodies

Serum samples were screened for human anti-mouse antibodies (HAMA) with a commercially available ELISA kit (HAMA ELISA medac; medac Diagnostika GmbH, Hamburg, Germany). The assay is a one-step sandwich enzyme immunoassay method, with a sensitivity ranging from 40 to 2,000 ng/mL. Briefly, a 1:5 dilution of patient serum and enzyme-labeled (horseradish peroxidase) mouse IgG were incubated for 30 min at 37°C on a microtiter plate pre-coated with mouse IgG. HAMA present in the serum bind to the solid phase and to the enzyme-labeled mouse IgG (bridge binding). After washing and addition of substrate, the optical densities of the complexes, measured at 450 nm, are directly proportional to the HAMA concentrations in serum.

Screening for the global human anti-idiotypic antibodies (human anti-chimeric antibodies) in serum was carried out using an idiotype-specific, two-step competitive ELISA method (anti-idiotypic ELISA; Novartis Pharma AG, Basel, Switzerland). Briefly, the assay is based on the competition between a fixed amount of fluorescein-labeled rabbit anti-idiotypic antibody and the human anti-idiotypic antibody possibly present in the serum sample for binding with a fixed amount of biotinylated basiliximab. Detection was performed using peroxidase-labeled sheep anti-fluorescein antibody and peroxidase substrate solution (ortho-phenylene-diamine/H₂O₂), with measurement of optical density at 490 nm. In the absence of anti-idiotypic antibody in the sample, the signal is maximum. The greater the amount of human anti-idiotypic antibody in the sample, the lower the signal. The assay range is 200 to 6,400 ng/mL.

RESULTS

Detection of Anti-basiliximab IgE Antibodies in Serum

No anti-basiliximab antibody was present at the time of the first or on the day of the second course of basiliximab therapy (Fig. 1). After the second exposure to basiliximab, specific IgE became readily detectable and persisted until the last assay 5 months after basiliximab reexposure. No reactivity against daclizumab was detected at any time. As controls, we tested sera from two children who underwent uneventful basiliximab therapy. There was no anti-basiliximab or anti-daclizumab reactivity detectable up to 3 months after treatment (optical densities, <55). Along the same line, no reactivity against basiliximab or daclizumab (optical densities, <70) was detected among control atopic patients who displayed high levels of IgE (n=5; mean IgE levels, 1,766 IU/mL; range, 366–5,750 IU/mL).

The Anti-basiliximab IgE Response Does Not Display Anti-murine Reactivity

As shown in Table 1, blocking the potential IgE anti-murine reactivity in the patient's sera by addition of optimal amounts of the unlabeled, control murine IgG2a mAb OKT3 did not prevent to any extent the later binding of biotinylated basiliximab. The absence of anti-murine IgE reactivity was further indicated by the inability of the patient's sera to bind biotinylated OKT3 (Fig. 2). Taken together, these results indicate that the anti-basiliximab IgE response has no anti-murine component and is therefore exclusively directed against basiliximab idiotypes.

Anti-basiliximab IgE Antibodies Are Present on Circulating Basophils

Blood harvested 9 months after the anaphylactic shock was tested in a biologic assay for the presence of basophil-bound IgE. A monoclonal anti-human IgE antibody that cross-links membrane-bound IgE and triggers the production of LT provided positive control by basophils. Addition of basiliximab to the patient's blood led to a dose-dependent LT production (Fig. 3). No consistent LT production was seen after exposure to daclizumab. No LT were produced by blood from two

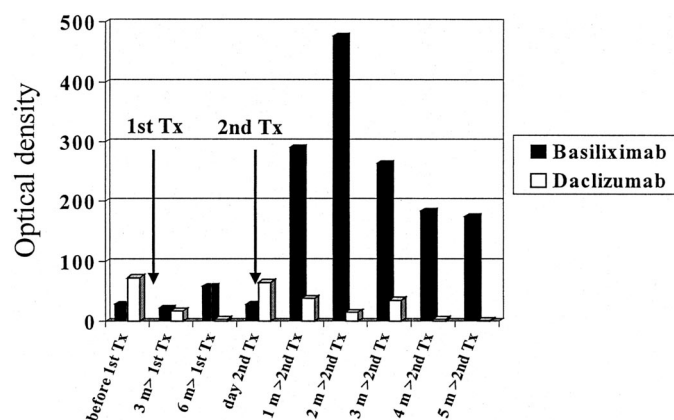


FIGURE 1. Presence of anti-basiliximab IgE antibodies in the serum. Sera from the patient were assayed at different time points with regard to his first and second renal transplantation. Serum IgE were captured on ELISA plates, and reactivity to biotinylated basiliximab and daclizumab was assayed.

TABLE 1. A control murine IgG2a monoclonal antibody does not prevent the binding of basiliximab to serum IgE

Preincubation with control murine IgG2a	Binding of basiliximab to serum IgE (optical density) ^a	
	Serum sampled 2 months after anaphylactic shock	Serum sampled 3 months after anaphylactic shock
Yes	283	281
No	287	277
Background ^b	45	55

^a Serum IgE were allowed to bind to anti-IgE coated plates, before sequential incubation with unlabeled control murine IgG2a mAb and biotinylated basiliximab.

^b Assay performed without the addition of biotinylated basiliximab.

healthy controls after addition of either daclizumab or basiliximab (<2% of the production triggered by the anti-IgE mAb).

Presence of Anti-basiliximab Idiotypic and Absence of Anti-murine Anti-isotypic Response

Considerable levels of anti-basiliximab antibody were present after the first exposure to basiliximab and on the day of the second transplantation and for months thereafter (Fig. 4). No anti-murine antibody was detected at any time, ruling out the presence of sensitization against murine isotypic determinants (Fig. 4).

DISCUSSION

We report here a case of IgE-mediated anaphylactic shock that took place after retreatment with basiliximab. The detection of an anti-basiliximab IgE response indicates that the reaction was truly anaphylactic rather than anaphylactoid, as in the latter case mast cells and basophils are activated by

non-IgE-mediated stimuli. IgE-mediated anaphylactic shock has been described on reexposure to the murine mAb OKT3 (11), but the present case seems to be the first description of IgE-mediated anaphylactic shock caused by basiliximab or by any chimeric or humanized mAb.

Sequential assays revealed that circulating anti-basiliximab IgE became apparent only after the second basiliximab injection, which triggered the anaphylactic shock. However, it is well known that the detection of specific IgE in blood is an inconstant finding in anaphylaxis. Indeed, anaphylaxis is initiated by the cross-linking of membrane-bound, allergen-specific IgE present on mast cells and basophils. IgE are retained there for prolonged periods after binding to high-affinity type I Fcε receptors. The observation that the patient's basophils harvested months after the anaphylactic shock were specifically and potently activated to produce LT in vitro on reexposure to basiliximab supports the hypothesis that basophils and mast cells displayed basiliximab-specific IgE at the time of the anaphylactic shock, even in the absence of circulating IgE.

One important clinical issue is whether the IgE anti-basiliximab response is cross-reactive to daclizumab, the other anti-IL-2R mAb used in the clinics. We found no evidence for daclizumab reactivity either by circulating or by basophil-bound IgE. Cross-reactivity was not expected on theoretical grounds, as the two parental antibodies originate from two distinct clones and therefore should bear distinct idiotypes. With regard to the fine specificity of the anti-basiliximab IgE response, our present data indicate reactivity directed exclusively against basiliximab idiotypes. First, we could not find any reactivity toward the murine isotypic determinants present on a control murine IgG2a mAb. Second, an anti-allotypic reactivity cannot be involved in this setting. Indeed, murine IgG2a allotype determinants are restricted to CH2 and CH3 immunoglobulin heavy chain domains (12, 13), and

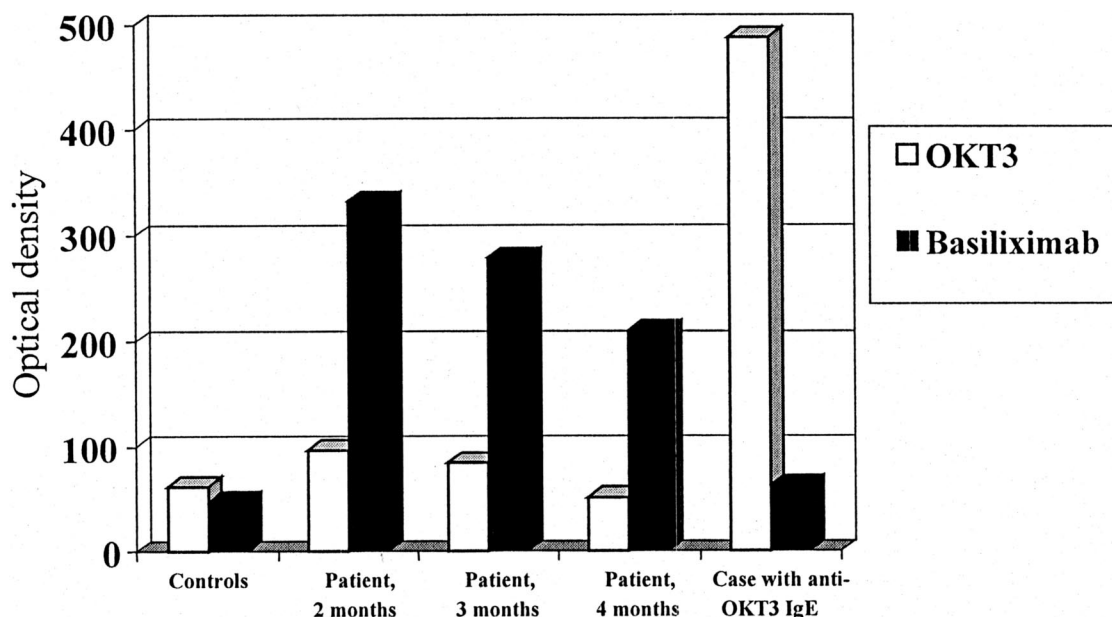


FIGURE 2. Anti-basiliximab IgE response: absence of anti-murine reactivity. Sera harvested 2, 3, and 4 months after the basiliximab-induced anaphylactic shock were assayed for IgE reactivity to basiliximab and to a control murine IgG2a mAb (OKT3). As a positive control for IgE reactivity against OKT3, we tested a serum known to contain anti-OKT3 IgE antibodies. The mean value of sera from two healthy controls is also shown

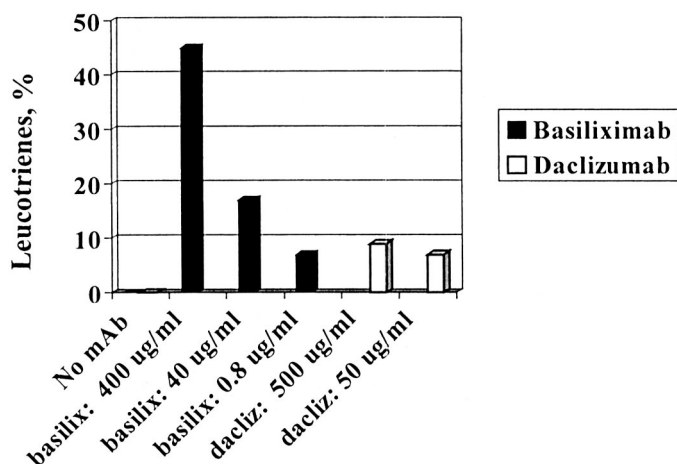


FIGURE 3. Basiliximab triggers LT production by the patient's basophils. Leukocytes from the patient, isolated 9 months after the anaphylactic shock, were incubated with basiliximab and daclizumab, and with an anti-IgE mAb as positive control. Background and anti-IgE-induced LT levels were 138 pg/mL and 883 pg/mL, respectively. Results are expressed as percentage of the value observed with the anti-IgE mAb.

these have been replaced by human IgG1 structure within the basiliximab mAb.

In addition to IgE, the patient also developed high titers of antibodies directed against basiliximab idiotypes. The lack of anti-murine reactivity by ELISA further confirms the exclusive anti-idiotypic specificity of the anti-basiliximab response. Although we did not characterize the Ig class responsible for this response, it is unlikely to be IgE. First, titers reached 10 mg/L, which is several orders of magnitude above classic specific IgE titers. Second, and contrary to the IgE response, this component of the anti-basiliximab sensitization was already present after the first exposure to basiliximab and was readily detectable on the day of the second transplantation. Presumably, IgG are responsible for this early, specific, high-titered anti-idiotypic reactivity. Blocking experiments indicated that the patient's serum was able to prevent the binding of basiliximab, but not of daclizumab, to IL-2R-positive lymphocytes (data not shown). This confirms the biologic activity of the anti-idiotypic reactivity, and fur-

ther indicates that it does not cross-react with daclizumab. The presence of a classic, blocking, anti-idiotypic sensitization together with IgE response is reminiscent of the universal occurrence of anti-idiotypic anti-OKT3 IgG sensitization among the 3% of patients who developed anti-OKT3 IgE antibodies (10).

The incidence and the risk factors for the development of an anti-basiliximab IgE response remain to be established. In the present case, one may speculate that the rapid discontinuation of all concomitant immunosuppression after the first basiliximab administration did contribute to sensitization. Indeed, it has been well demonstrated that both CsA and mycophenolate mofetil reduce the sensitization to polyclonal and monoclonal antilymphocyte agents. In keeping with this hypothesis, it is noteworthy that the previously reported patient who developed an IgE-mediated anaphylactic shock on reexposure to OKT3 also had his immunosuppressive drugs rapidly withdrawn during the first OKT3 course because of early graft loss from thrombosis (11). Along the same line, the single patient who developed an anti-idiotypic response to basiliximab in an early trial had his immunosuppressive therapy stopped at day 9 because of renal artery thrombosis (14).

On practical grounds, what measures should be considered for patients who are candidates for basiliximab retreatment? Those in whom immunosuppressive therapy was stopped early because of graft failure should probably not receive basiliximab again, unless IgE sensitization can be ruled out. The use of the alternate anti-IL-2R mAb in these patients appears a better choice, because there seems to be no cross-sensitization between the two mAb. However, despite the fact that a cross-sensitization between these two antibodies can be ruled out in the patient reported here, one cannot exclude that a cross-sensitization may occur in other cases. Therefore, detection of anti-basiliximab and anti-daclizumab IgE antibodies on circulating basophils could be useful in this setting. Alternatively, intradermal testing with the anti-IL-2R mAb could reveal sensitization, as recently described in a patient who developed anaphylaxis to basiliximab (15). For those whose tests are negative, an intravenous test dose with full resuscitation at hand could be the next step. As a general measure, reexposure to the same mAb for iterative transplantation should be performed with caution, preferably in the operating room after the induction of narcosis.

REFERENCES

1. Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients: CHIB 201 International Study Group. *Lancet* 1997; 350(9086): 1193.
2. Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation: Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998; 338(3): 161.
3. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody: United States Simulect Renal Study Group. *Transplantation* 1999; 67(2): 276.
4. Nashan B, Light S, Hardie IR, et al. Reduction of acute renal allograft rejection by daclizumab: Daclizumab Double Therapy Study Group. *Transplantation* 1999; 67(1): 110.
5. Ponticelli C, Yussim A, Cambi V, et al. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001; 72(7): 1261.
6. Sollinger H, Kaplan B, Pescovitz MD, et al. Basiliximab versus antithy-

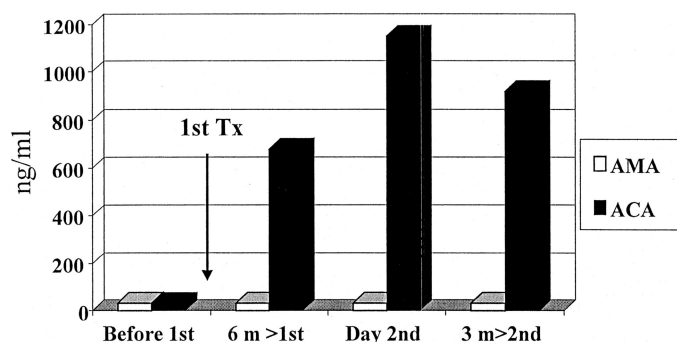


FIGURE 4. Presence of anti-chimeric antibodies and absence of anti-murine antibodies after basiliximab exposure. Sera from the patient were assayed at different time points with regard to his first and second renal transplantation.

- mocyte globulin for prevention of acute renal allograft rejection. *Transplantation* 2001; 72(12): 1915.
7. Amlot PL, Rawlings E, Fernando ON, et al. Prolonged action of a chimeric interleukin-2 receptor (CD25) monoclonal antibody used in cadaveric renal transplantation. *Transplantation* 1995; 60(7): 748.
 8. Vincenti F, Lantz M, Birnbaum J, et al. A phase I trial of humanized anti-interleukin 2 receptor antibody in renal transplantation. *Transplantation* 1997; 63(1): 33.
 9. Kovarik J, Wolf P, Cisterne JM, et al. Disposition of basiliximab, an interleukin-2 receptor monoclonal antibody, in recipients of mismatched cadaver renal allografts. *Transplantation* 1997; 64(12): 1701.
 10. Abramowicz D, Crusiaux A, Niaudet P, et al. The IgE humoral response in OKT3-treated patients: Incidence and fine specificity. *Transplantation* 1996; 61(4): 577.
 11. Abramowicz D, Crusiaux A, Goldman M. Anaphylactic shock after retreatment with OKT3 monoclonal antibody. *N Engl J Med* 1992; 327(10): 736.
 12. Dognin MJ, Lauwereys M, Strosberg AD. Multiple amino acid substitutions between murine gamma 2a heavy chain Fc regions of Ig1a and Ig1b allotypic forms. *Proc Natl Acad Sci USA* 1981; 78(7): 4031.
 13. Oi VT, Herzenberg LA, Birshtein BK. Localization of murine Igh-1a allotypic determinants by using a panel of mouse myeloma variant immunoglobulins. *J Immunol* 1983; 130(4): 1967.
 14. Kovarik JM, Rawlings E, Sweny P, et al. Prolonged immunosuppressive effect and minimal immunogenicity from chimeric (CD25) monoclonal antibody SDZ CHI 621 in renal transplantation. *Transplant Proc* 1996; 28(2): 913.
 15. Leonard PA, Woodside KJ, Gugliuzza KK, et al. Safe administration of a humanized murine antibody after anaphylaxis to a chimeric murine antibody. *Transplantation* 2002; 74: 1697.

0041-1337/03/7603-463/0

TRANSPLANTATION

Copyright © 2003 by Lippincott Williams & Wilkins, Inc.

Vol. 76, 463–470, No. 3, August 15, 2003

Printed in U.S.A.

A COMPARISON OF DISCHARGE IMMUNOSUPPRESSIVE DRUG REGIMENS IN PRIMARY CADAVERIC KIDNEY TRANSPLANTATION

WIDA S. CHERIKH,¹ H. MYRON KAUFFMAN,¹ JUDE MAGHIRANG,¹ ANTHONY J. BLEYER,² AND CHRISTOPHER P. JOHNSON³

Background. Finding the best combination of immunosuppression is an important challenge in kidney transplantation. Current short-term (1- and 3-year) allograft survival is quite good, making it difficult to determine differences in therapeutic regimens without large sample sizes. Using data from the United Network for Organ Sharing/Organ Procurement and Transplantation Network database, the current study provides substantial statistical power to analyze the outcomes for different immunosuppressive regimens.

Methods. To compare the effects of four discharge regimens (cyclosporine and azathioprine [CYA+AZA], CYA and mycophenolate mofetil [MMF], tacrolimus [TAC]+AZA, and TAC+MMF) on long-term survival, a multivariate Cox regression analysis was conducted on 19,246 primary cadaveric kidney transplants during 1995 to 1998.

Results. Compared with CYA+AZA, the combination of CYA+MMF was associated with a 10% reduced risk of graft loss (relative risk [RR] 0.90, 95% confidence limit [CL] 0.84–0.96, $P < 0.001$), whereas TAC+AZA was associated with an 18% reduced risk (RR 0.82, 95% CL 0.67–1.005, $P = 0.06$) and TAC+MMF with a 20% reduced risk of graft loss (RR 0.80, 95% CL 0.71–0.89, $P < 0.001$). All three regimens benefited patients regardless of delayed graft function (DGF) or early acute rejection status. In addition, in the absence of DGF, the combinations of CYA+MMF, TAC+AZA, and TAC+MMF were associated with a reduced risk of mortality compared with CYA+AZA.

Conclusions. The major finding of this study was improved graft and patient survival associated with TAC+MMF and CYA+MMF in patients with or without DGF or early acute rejection.

Portions of this paper were presented at the annual meeting of the American Transplant Congress in Washington DC, April 27 to May 1, 2002.

This work was funded by the Health Research Services Administration contract #231-00-0115 and the United Network for Organ Sharing.

¹ Research Department, United Network for Organ Sharing, Richmond, VA.

² Internal Medicine/Nephrology Department, Wake Forest University School of Medicine, Winston-Salem, NC.

³ Division of Transplant Surgery, Medical College of Wisconsin, Milwaukee, WI.

⁴ Address correspondence to: Dr. CheriKh, 700 North 4th Street, Richmond, VA 23219. E-mail: cherikws@unos.org.

Received 19 November 2002. Accepted 10 April 2003.

DOI: 10.1097/01.TP.0000079839.38844.09

Short-term and long-term cadaveric kidney graft survival in the United States has progressively improved from 1988 to 1996 (1) in spite of the increased use of expanded criteria donors (2). Although the reasons for increased graft survival are multifactorial, reductions in the incidence of acute rejection have played a prominent role (1). The reduction in rejection episodes has most likely been because of new immunosuppressive agents or better use of existing drugs. In 1988, the combination of cyclosporine (CYA), azathioprine (AZA), and prednisone, with or without monoclonal or polyclonal antibody induction, was used in 70% of patients (3). Since that time, there has been increasing use of two newer agents: tacrolimus (TAC) and mycophenolate mofetil (MMF). Two reports using the United Network for Organ Sharing/Organ