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A prospective, double-blind, randomized study of high-versus low-dose OKT3 induction immunosuppression in cadaveric renal transplantation

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Abstract We undertook a prospective, double-blind study of high-(5-mg) versus low-(2-mg) dose OKT3 for induction immunosuppression (12 days) in cadaveric renal allograft transplantation. Maintenance immunosuppression was identical in both groups and consisted of azathioprine and prednisone initially, with cyclosporine beginning on the 5th postoperative day. Twenty-six patients were randomized. The groups were similar in terms of age, kidney ischemia time, peak PRA, and latest PRA. There were more diabetics and women in the high-dose group. Patient survival at 12 months was 100 % in both groups. Graft survival at 12 months was 92 % and 100 % in the high- and low-dose groups, respectively. Infections were mostly minor and equal in frequency in the two groups. All patients receiving high- or low-dose OKT3 had manifestations of the cytokine release syndrome; these were delayed in onset in the low-dose group. Eleven patients (85 %) in each group produced anti-OKT3 antibodies. Lymphocyte depletion after 1 day was major (> 98 %) and identical in both groups. CD3 antigens were removed more slowly in the low-dose group but eventually at equal rates in both groups. Cost was significantly lower in the low-dose group. We conclude that while both doses of OKT3 were effective and safe for induction immunosuppression, it may be prudent to use a lower dose of OKT3 for induction immunosuppression because of its potential to reduce cytokine-mediated effects and to avoid the complications of overimmunosuppression and because of the lower costs associated with it.

Key words OKT3, dose, renal transplantation · Kidney transplantation, OKT3, dose Immunosuppression, OKT3, dose

Introduction

OKT3 (muromonab CD3) is an IgG2a monoclonal antibody directed to the epsilon chain of the CD3 complex found adjacent to the receptor for antigen exclusively on peripheral blood and thymic medullary T lymphocytes [10]. Its powerful ability to prevent [16] and reverse [17] rejection of renal allografts in combination with other immunosuppressive drugs is well known.

Our own experience has suggested that the proper dose of OKT3 for preventing rejection has not yet been established [15]. Regimens of either 5 mg OKT3 per day for 14 days (total dose 70 mg) or 1 mg for 2 days, followed by 2 mg for 10 days (total dose 22 mg), also employing standard triple therapy (cyclosporin, azathioprine, and prednisone), appeared similarly effective in preventing rejection (7 % vs 8 %, respectively, incidence of rejection in the initial 2 weeks after transplantation) and were superior to a regimen consisting of standard triple therapy alone. However, a short course (5 days) of OKT3 was less effective than either longer one, as reflected by the 2-week rejection rate of 29 %. The use of a

lower dose (2 mg) of OKT3 was particularly attractive to us because of the potential for lower costs and less severe manifestations of the cytokine release syndrome [4, 12], mediated by cytokines [1] and well known to accompany the use of OKT3 in virtually all patients receiving it [13].

While we had substantial supportive evidence that a low dose of OKT3 (2 mg) was equivalent to a higher dose (5 mg) for immunosuppression induction, these comparative data were obtained at different times during a 5-year period that saw changes in cyclosporin dosing, organ retrieval, and preservation and recipient care.

Therefore, in order to compare the two regimens that had been shown to be equivalent historically, a double-blind, randomized, prospective study was designed and implemented. The results of this study show that a low dose of OKT3 for induction immunosuppression is as effective as a high dose, while being less expensive.

Methods

Patients

The patients participating in this study were transplanted at the Oregon Health Sciences University (OHSU) between 1 July 1990 and 15 August 1991. All patients who met the study criteria were invited to participate in the study unless a problem with adequate follow-up was anticipated. Twenty-six patients, whose demographics are shown in Table 1, were entered in the study.

Study entrance criteria

Only first cadaveric transplant recipients between the ages of 18 and 50 years whose cadaveric kidneys had an ischemia time of 36 h or less and came from a donor whose age was between 10 and 50 years were allowed to participate in the study. These entrance criteria were chosen to minimize both recipient and donor factors that could lead to graft dysfunction or loss due to nonimmunological causes. We felt that if, in fact, there were any gross differences between the protocols due to under- or overimmunosuppression, they would be evident in this group of patients.

Randomized, double-blind study

The study was randomized and double-blinded. Neither the patients, the nurses, nor the doctors caring for the patients knew which dose of OKT3 the patients received. The pharmacy kept the randomization schedule and made up the OKT3 in a 5-ml volume, regardless of the dose. The patients were randomized in blocks of four patients (two with high-dose OKT3 and two with low-dose OKT3). Only a single research associate in the Immunogenetics Laboratory whose responsibility it was to maintain the clinical and laboratory records of these patients was kept unblinded. The study was reviewed and approved by the OHSU Institutional Review Board and all patients signed consent forms before entering the study. An oversight committee consisting of a statistician, a community nephrologist, an infectious disease specialist, a transplant physician from a different organ transplant program, and a pathologist reviewed the protocol before the study and reviewed the results at the halfway point and at the end of the study. None of these individuals was directly involved with the kidney transplant program at OHSU.

Protocols

Patients randomized to the high-dose OKT3 group received 5 mg OKT3 daily, beginning in the operating room, for a total of 12 doses (total 60 mg). Patients randomized to the low-dose OKT3 group received 1 mg OKT3 for 2 days, beginning in the operating room, followed by 2 mg OKT3 daily for 10 days (total 22 mg). Patients in both groups received the identical maintenance immunosuppression regimen consisting of cyclosporin, 7 mg/kg per day, beginning on the 5th postoperative day; azathioprine, 5 mg/kg i.v. pretransplantation, followed by 2 mg/kg per day post-transplantation; methylprednisolone, 500 mg i.v. in the operating room and 125 mg i.v., b.i.d., on the 1st postoperative day; and prednisone, 1 mg/kg per day, beginning on the 2nd postoperative day, being tapered by 0.1 mg/kg each day until a dose of 0.5 mg/kg per day was reached and then further tapered to 0.4 mg/kg per day at the end of the 1st month and to 0.3, 0.2, 0.15, and 0.1 mg/kg per day at the end of subsequent months. Acute rejection episodes were documented with a biopsy when possible and were treated with an oral steroid pulse (5 mg/kg per day for 5 days, followed by a 3-day taper) or, if resistant to steroids, by OKT3 (5 mg/day for 10 days) or Minnesota antilymphoblast globulin (MALG, 15 mg/kg per day for 10 days).

Standard pre- and postoperative procedures

Panel reactive antibody (PRA) was determined with a 48-member panel of lymphocytes selected to represent as many of the known HLA antigens as possible and using a standard (NIH) microlymphocytotoxic technique. Pretransplant crossmatches included a standard NIH, as well as antiglobulin-enhanced and B-cell crossmatches [11, 18]. Any activity above background was considered a contraindication to transplantation. In all patients anesthesia was induced with sodium thiopental and maintained with nitrous oxide, isofluorane, and oxygen with fentanyl supplementation. Muscle relaxation was maintained with a variety of nondepolarizing muscle relaxants. Postoperative analgesia was routinely achieved with morphine sulfate. Routine postoperative medications consisted of a second generation cephalosporin for 48 h, mini-dose subcutaneous heparin, ranitidine, and appropriate hypertension and glycemic control. CMV-seronegative patients with diabetes were given kidneys only from seronegative donors according to a protocol in practice for the past 5 years at our center. (According to this protocol, patients 50 years of age or older must also be seromatched for CMV, but none of these were entered into this study). All CMV-seronegative recipients who did receive a kidney from a seropositive donor were given prophylactic acyclovir, according to the Balfour protocol [2]. Patients with a history of herpes simplex infections were also given prophylactic acyclovir (200 mg p.o., b.i.d.). Dialysis was initiated when hyperkalemia, volume overload, oliguria, or a rising blood urea nitrogen (BUN) and creatinine warranted it.

Clinical follow-up

Information was collected and recorded on all patients regarding delayed graft function (defined as dialysis in the 1st week), rejection incidence and timing, side effects of OKT3 (cytokine release syndrome), vital signs, infections, and the cost of OKT3. Mean arterial blood pressure was calculated using the formula:

$$\text{BP Diast} + \left(\frac{\text{BPsyst} - \text{BPdiast}}{3}\right)$$

Table 1 Patient demographics

	High-dose protocol ($N = 13$)	Low-dose protocol ($N = 13$)
Males (%)	39*	85*
Mean recipient age (years)	39	37
Mean donor age (years)	30.6	35.8
Diabetics (%)	31	8
Mean cold ischemia time (h)	26	27
Mean peak PRA	8.3	7.3
Mean latest PRA	0.15	0.62
Median number of transfusions	1	1
HLA A, B Mismatches (antigen)	2.1	2.9
HLA DR Mismatches (antigen)	1.2	1.3

* $P < 0.05$

Table 2 Side effects[a]

	High-dose protocol ($N = 11$)	Low-dose protocol ($N = 10$)
Anorexia	5	5
Nausea	6	5
Headache	5	5
Vomiting	3	4
Diarrhea	4	6
Weakness	4	2
Dyspnea	1	2
Pulmonary edema	1	1
Hallucinations	1	1

[a] Side effect profile data collection forms were lost for five patients

Monitoring

Human anti-mouse antibody (HAMA) was measured using a standard ELISA assay [14]. OKT3 pharmacodynamics were measured using anti-CD2 (OKT11) and anti-CD3 (Leu4A) monoclonal antibodies, a flow cytometer (FACScan, Becton-Dickinson, San Jose, Calif.), and techniques that measure CD3 antigen density on T cells and absolute number of CD2-positive or CD3-positive T cells per mm^3 [7]. All of the monitoring was also kept blinded from the physicians and nurses managing the patients. Only the single research associate in the laboratory had access to these results until after the study had been completed.

Statistics

Actuarial graft and patient survival rates were determined and compared using the log rank test. Other comparisons were made using a two-tailed Fischer's exact test.

Results

Demographics

By chance more men (85 %) were randomized to the low-dose protocol than to the high-dose protocol (39 %, $P < 0.05$). Otherwise, there were no statistically significant differences between the two groups for recipient age, donor age, percent diabetes, kidney cold ischemia time, peak PRA, latest PRA, number of transfusions, HLA A, B mismatch, or HLA DR mismatch (Table 1).

Delayed graft function

Thirty-eight percent of the high-dose and 31 % of the low-dose group had delayed graft function (P = NS).

Cytokine release syndrome (CRS) side effects

The CRS side effects encountered were anorexia, nausea, headache, vomiting, diarrhea, weakness, dyspnea, pulmonary edema, and hallucinations. These occurred with equal frequency in the two groups (Table 2).

During the 1st week a temperature of 38.5 °C or higher occurred on 35/77 (46 %) days in the high-dose OKT3 group and on 25/77 (33 %) days in the low-dose OKT3 group (P = NS). The fever occurred later in the low-dose group when the dose was converted from 1 mg to 2 mg OKT3.

The mean maximum and minimum arterial blood pressures were determined on each day of therapy during the 1st week of OKT3 treatment. The mean minimum arterial blood pressure fell to or below 90 mm Hg on 31/80 (39 %) days in the high-dose group and on 15/80 (19 %) days in the low-dose group ($P < 0.02$). The mean maximum arterial blood pressure fell to or below 100 mmHg on 16/80 (20 %) days in the high-dose group and on 9/80 (11 %) days in the low-dose group (P = NS).

Rejection incidence, graft survival and function, and patient survival

The kidney allograft of one patient in the high-dose group failed due to an intrarenal clotting event during the 2nd postoperative week. However, no rejection was found in the surgically removed specimen. None of the other 12 high-dose OKT3 patients had a rejection episode during the first 3 postoperative months (rejection incidence at 12 weeks 0 %). Two of 13 low-dose OKT3 patients had rejections treated during the first 3 postoperative months (rejection incidence at 12 weeks 15 %, P = NS). The mean serum creatinine levels at 1 month and 12 months post-transplantation were 1.7 and 1.8 mg/dl in the low-dose group and 1.5 and 1.5 mg/dl in the high-dose group (P = NS).

All patients have been followed for at least 12 months since transplantation and are alive (patient survival 100 %, both groups; mean follow-up 19 months, range 12–24 months). Only one graft was lost (high-dose

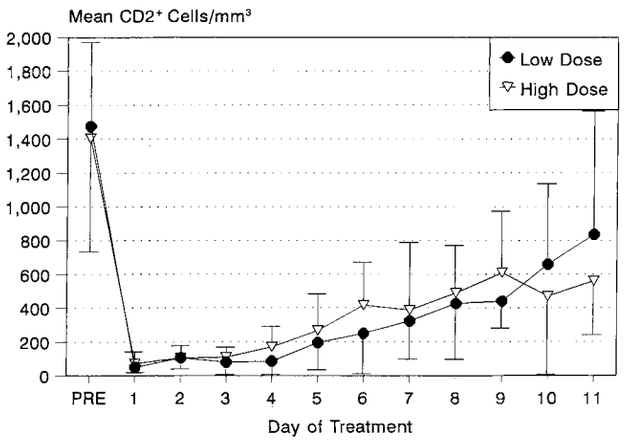

Fig. 1 Mean number of $CD2^+$ cells/mm^3 ± 1 SD. Before each OKT3 dose, the absolute number of $CD2^+$ cells was determined using flow cytometry and FITC-labelled OKT 11 as a CD2 marker. Shown here are the mean values for the high- and low-dose groups ($N = 13$ in each group) on each day of treatment. This number was derived using the formula: percent $CD2^+$ cells × percent lymphocytes × WBC/mm^3

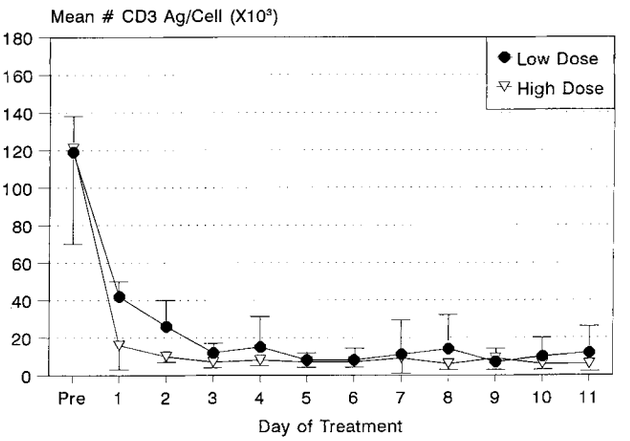

Fig. 3 Mean number of CD3 Ag/cell ($\times 10^3$) ± 1 SD. Before each OKT3 dose, the mean number of CD3 antigens per T cell was calculated using a method published elsewhere [17]. Shown here are the mean values for the 13 patients in each group on each day of treatment

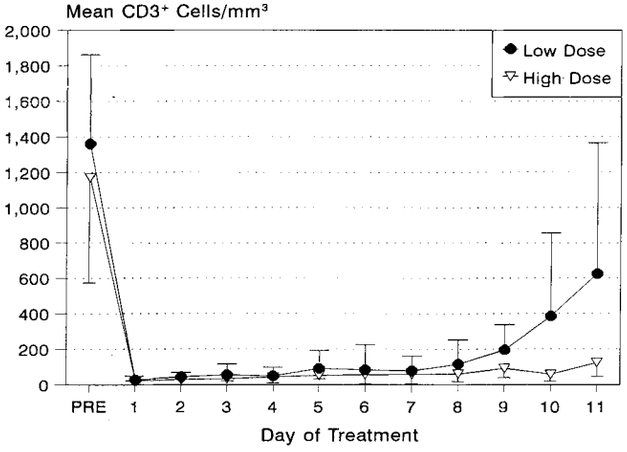

Fig. 2 Mean number of $CD3^+$ cells/mm^3 ± 1 SD. Before each OKT3 dose, the absolute number of $CD3^+$ cells was determined using flow cytometry and FITC-labelled Leu4A as a CD3 marker. Shown here are the mean values for the high- and low-dose groups ($n = 13$ in each group) on each day of treatment

group) during the first 12 months following transplantation (actual 12-month graft survival rates 92 % in the high-dose and 100 % in the low-dose group, P = NS).

Infections

Three of four (75 %) and one of three (33 %) patients in the high- and low-dose groups, respectively, who were at risk for primary CMV disease developed it (P = NS). The incidences of herpes infections (1/13 in high-dose group; 2/13 in low-dose group), upper respiratory infections (2/13 in high-dose group; 6/13 in low-dose group), bacterial infections (6/13 in high-dose group; 7/13 in low-dose group) and fungal infections (2/13 in high-dose group; 2/13 in low-dose group) were all minor and did not differ significantly.

Pharmacodynamics of OKT3

T cells were monitored for the predicted effects of OKT3 on their numbers and on CD3 modulation. One milligram of OKT3 was equally as effective as 5 mg for depleting T cells from the peripheral blood compartment (Fig. 1). During therapy, CD2-positive cells returned to the circulation in similar numbers and at similar rates in the two groups. The numbers of cells with a minimum number of detectable CD3 molecules were identical in the two groups until after the eighth OKT3 dose (Fig. 2). At that point, the number of CD3-positive cells increased gradually in the low-dose group but remained low in the high-dose group. However, the number of CD3 molecules on the T cells remained minimal even at the end of therapy in both the high- and low-dose groups (Fig. 3). The rate of CD3 modulation from T cells was slower in the low-dose group (42×10^3 vs 16×10^3 molecules after the first dose and 26×10^3 vs 10×10^3 molecules after the second dose), but after the third dose the mean antigen density was below 15×10^3 in both groups compared to 120×10^3 prior to treatment.

Human anti-mouse antibody (HAMA) production

The incidence and titer of anti-OKT3 antibody production was not significantly different between the two groups. Eighty-three percent and 85 % of the high- and low-dose groups, respectively, were found to have HAMA. Two of ten (20 %) patients in the high-dose group with HAMA had a titer of 1 : 1000 or more while 4/11 (36 %) of the patients in the low-dose group developed this level of antibodies. The remaining eight and seven patients in the high- and low-dose groups, respectively, had HAMA titers of 1 : 1000.

Cost of OKT3

The pharmacy cost per patient for the course of OKT3 was U.S. $ 5,334.23 for the high-dose group and U.S. $ 2,696.15 for the low-dose group.

Discussion

Since 1989, all first cadaver kidney recipients (and regrafted patients who had not received OKT3 before) have been given the low-dose OKT3 induction immunosuppression protocol as standard therapy. We believe that avoidance of early rejection episodes will benefit patients over the long term and that OKT3 – especially in lower doses – does not put patients at an unwarranted risk of infection or lymphoma.

Because, in our view, the proper dose of OKT3 had not been established, we undertook this randomized study. Low-risk patients were chosen to minimize nonimmunological causes of graft dysfunction or loss so that gross differences between the protocols, if present, could be more easily detected. The sample size for this study was small ($n = 26$ patients), but it was allowed because we had had extensive experience with both protocols, which seemed approximately equivalent. The sample size required to demonstrate equivalency of the protocols regarding rejection incidence and graft survival was much too large for a single center alone to study. However, in our experience and as corroborated elsewhere [16], the rejection incidence of both protocols was clearly and significantly lower than that of triple therapy with cyclosporin, azathioprine, and prednisone without antibody induction. We believed that the study of side effects, T-cell pharmacodynamics, and HAMA would be very valuable, even with a small patient group, because such a detailed comparison had never before been performed.

Both the high- and the low-dose OKT3 immunosuppression induction protocols led to excellent 1-year patient (100 %) and graft (92 % and 100 %) survivals and a low 3-month rejection rate (0 % and 15 %). The low-dose approach was found to be significantly superior in two ways: cost and blood pressure response. First, by prescribing approximately 37 % of the amount of OKT3 used in the high-dose protocol (22 mg vs 60 mg), the pharmacy costs were reduced by 49 % ($ 2,696. vs $ 5,334.). The actual charges to the patient were reduced by a greater dollar amount because of the usual mark-up engaged in by all hospital pharmacies. The other hospital and outpatient charges for the two groups were similar. Secondly, there was significantly less hypotension in the low-dose group. Hypotension following OKT3 use is thought to be mediated by cytokines that cause a reduced systemic vascular resistance (SVR) and perhaps direct or indirect myocardial depression [5, 9]. The mean arterial blood pressure (MABP) fell to or below 90 mm Hg on 39 % compared to only 19 % of the days during the 1st week in the high- versus the low-dose group, respectively ($P < 0.02$). The only patient who lost a graft in the 1st year in either group was a woman with diabetes on the high-dose protocol whose MABP fell to 73 mm Hg and was at or below 90 mm Hg during 4 of the first 7 days following transplantation. Her graft failed as a result of an intrarenal clotting event without evidence of rejection. A confounding issue was the significantly greater number of women in the high-dose group (61 % vs 15 %), which could possibly explain the lower MABP seen in that group.

There were three measurements of outcome that favored the low-dose protocol but were not statistically significant, perhaps because of the small number of patients. First, OKT3 is associated with a reversible nephropathy ("cytokine nephropathy") that has been seen both with induction immunosuppression [3] and when used for treatment of rejection [6, 13]. Cytokines released by OKT3 might increase the incidence of delayed graft function (DGF). In fact, the incidence of DGF was 25 % higher in the high-dose OKT3 group than in the low-dose group. Second, the febrile response following OKT3 is cytokine-mediated, and there was a trend toward less fever in the low-dose OKT3 group. The number of days during the 1st week on which the body temperature was 38.5 °C or above was 40 % higher in the high-dose than in the low-dose group. Third, the numbers of patients at risk for primary CMV infections were four and three in the high- and low-dose groups, respectively. The incidence of symptomatic CMV disease was 127 % higher among these patients in the high-dose versus the low-dose group.

There were three outcome measurements that might have favored the high-dose protocol. First was the CD3 antigen density profile. CD3 was removed from the T cells more slowly in the low-dose group (Fig. 3), and having a greater amount of CD3 on T cells might have allowed them to retain some immunocompetence. However, it is important to note that the higher T-cell CD3 density occurred when there were few, if any, T cells detectable in the peripheral blood compartment (Fig. 1).

Despite this, we have now changed our low-dose protocol to consist of 2 mg OKT3 throughout the course instead of beginning with 1 mg for 2 days. Two milligrams modulate CD3 to a degree nearly identical to that of 5 mg [8]. Second, in some patients on the low-dose protocol, T cells bearing low-density CD3 were found in increasing numbers toward the end of treatment. These were patients who made early HAMA, which complexed and neutralized some of the OKT3, allowing the emergence of CD3 in small amounts on T cells. This was not a problem for early HAMA producers in the high-dose group because of an excess of OKT3 in the serum of these patients. The increased numbers of low-density, CD3-bearing T cells in the low-dose group might have been responsible for the only two rejection episodes occurring in the low-dose group (there were none in the high-dose group). Accordingly, for those few patients who begin to express CD3 at the end of therapy, we now increase the dose by 1 mg/day. In most cases, a total of 3 mg is sufficient to counteract the HAMA. Third, there was a trend toward a greater number of high-titer HAMA responses in the low-dose group (31 % vs 17 %), and at 3 months 11 % of the high-dose group and 62 % of the low-dose group still had detectable HAMA. This difference could be explained by the low-dose protocol being less immunosuppressive, which in part is what we hoped to achieve by using less OKT3, to result in fewer complications. Reducing the CD3 density by adding additional milligrams at the beginning of the protocol (2 mg vs 1 mg) in our new protocols might obviate this problem.

The usual side effect profile ("flu-like" symptoms) occurred in both the high- and low-dose groups and made it virtually impossible to guess which patients received which dose of OKT3. While not available during the study, the total T-cell profiles (measured using an anti-CD2 monoclonal antibody) were nearly identical and could not have been used prospectively or retrospectively to differentiate the two groups (Fig. 1).

This first-of-a-kind, double-blind study of high-versus low-dose OKT3 for induction immunosuppression indicates that the proper dose of OKT3 had not been previously established and that lower doses of OKT3 are effective and might be safer.

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