Transpl Int (1994) 7: 258–263

ORIGINAL ARTICLE

Daniel Abramowicz
Michel Goldman
Olivier Mat
Gerrie Estermans
Alain Crusiaux
Jean-Louis Vanherweghem
Luc De Pauw
Paul Kinnaert
Pierre Vereerstraeten

OKT3 serum levels as a guide for prophylactic therapy: a pilot study in kidney transplant recipients

Received: 13 July 1993
Received after revision: 23 November 1993
Accepted: 6 December 1993

D. Abramowicz (✉) · O. Mat
J.-L. Vanherweghem · L. De Pauw
P. Kinnaert · P. Vereerstraeten
Department of Nephrology, Dialysis and Transplantation, Hopital Erasme, 808 Route de Lennik, B-1070 Brussels, Belgium

M. Goldman · A. Crusiaux
Department of Immunology, Hopital Erasme, 808 Route de Lennik, B-1070 Brussels, Belgium

G. Estermans
Cilag Benelux, Belgium

Abstract The use of OKT3 as prophylaxis in renal transplantation results in a reduced incidence of graft rejection and appears to have beneficial effects on long-term kidney graft survival. However, we and others have observed that patients still experience rejection during the period of OKT3 prophylaxis given at the regular 5 mg/day dose. Many of these patients had no circulating $CD3^+$ cells at the time of rejection, but their OKT3 serum levels were distinctly low (< 500 ng/ml). This led us to adjust OKT3 doses (5 or 10 mg) daily, according to the patients' OKT3 levels, in order to maintain an OKT3 concentration of around 1000 ng/ml. In addition, patients were randomized to receive either 5 mg (group 1, $n = 15$) or 10 mg (group 2, $n = 14$) OKT3 as the initial three doses. Concomitant immunosuppression consisted of azathioprine and steroids, with the introduction of cyclosporin A on day 11. Patient survival was 100 % after 3 months of follow-up. The intensity of OKT3 first-dose reactions was similar in both groups. Intragraft thrombosis, initially observed in a previous group of patients who received a fixed 10 mg/day OKT3 prophylaxis, occurred in three patients in group 1 and resulted in two graft losses. The cumulative OKT3 dose was similar in both groups (mean ± SEM 98 ± 2 mg in group 1 vs 102 ±3 mg in group 2) and higher than the 70 mg usually administered. Group 2 patients had higher OKT3 serum levels during the first 4 days of therapy. No correlation could be found between patient weight and cumulative OKT3 dose ($r = 0.29$). No patient in either group 1 or 2 experienced rejection during OKT3 therapy. This compared favorably with an historical group of kidney recipients treated with a fixed 5 mg/day OKT3 dose, as 6 out of 32 patients in this group developed rejection ($P = 0.045$). The rejection rate up to 3 months post-transplantation in pooled group 1 and 2 patients was low (six episodes per 81 patient-months of risk exposure). We conclude that adaptation of the OKT3 dose according to daily OKT3 levels is safe and allows for excellent prevention of early graft rejection.

Key words Kidney transplantation, OKT3, prophylaxis · OKT3, kidney transplantation · Prophylaxis, OKT3, kidney transplantation

Introduction

The use of OKT3 as prophylaxis in renal transplantation results in a lower incidence of early graft rejection than occurs with cyclosporin A (CyA) regimens [2, 6, 17, 20, 21, 23, 29, 30]. In addition, two recent randomized studies, as well as data from the UNOS scientific registry, indicate that OKT3 prophylaxis has beneficial effects on kidney graft survival, especially in high-risk patients [2, 7, 23]. Nevertheless, rejections still occur during the period of prophylactic OKT3 administration (5 mg/day) in an estimated 10 %–20 % of patients [2, 19, 23]. This is of concern since, in a previous series of 66 patients treated with the fixed 5 mg/day protocol, 12 patients developed early graft rejection, 5 of whom lost their renal transplant in the ensuing months. Early rejections have initially been observed when $CD3^+$ cells reappeared in blood as a consequence of anti-OKT3 immunization [10, 31]. More

Table 1 Characteristics of the patients (P = NS for all parameters)

	OKT3 Induction dose	
	Group 1 (3 × 5)	Group 2 (3 × 10)
No. of patients	15	14
Age (years) of recipients (mean ± SEM)	40.6 ± 1.9	40.6 ± 3.5
Age (years) of donors (mean ± SEM)	36.0 ± 3.0	30.4 ± 4.0
No. of recipients of first graft	14	12
No. of recipients with anti-HLA immunization	2	3
No. of blood transfusions per recipient (mean ± SEM)	4.4 ± 1.2	3.4 ± 1.1
Cold ischemia time (h; mean ± SEM)	25.3 ± 2.0	24.3 ± 1.8
Warm ischemia time (min; mean ± SEM)	30.4 ± 2.3	31.3 ± 1.8
HLA antigen incompatibilities (mean ± SEM)		
A	0.80 ± 0.20	0.93 ± 0.25
B	0.53 ± 0.17	0.86 ± 0.14
DR	0.07 ± 0.07	0.07 ± 0.07

recently, it appeared that rejection episodes could also occur in the absence of either circulating $CD3^+$ cells or anti-OKT3 antibodies [14, 18]. OKT3 serum levels were distinctly low at the time of rejection in these patients, so this parameter appears to be a critical risk factor for early rejection [14, 18]. These observations led us to adapt OKT3 doses on a daily basis in order to maintain OKT3 serum levels at around 1000 ng/ml. In addition, patients were randomized to receive either 5 or 10 mg OKT3 for the initial three doses. The present report describes the main biological and clinical parameters of the patients treated with these regimens.

Materials and methods

Patients and immunosuppressive regimens

Twenty-nine kidney transplant recipients were randomly allocated to receive either 5 mg (group 1, $n = 15$) or 10 mg (group 2, $n = 14$) OKT3 as their first three daily doses, from the day of surgery to postoperative day (POD) 2. The characteristics of the patients were similar in both groups (Table 1). The first OKT3 dose was injected intraoperatively, and OKT3 therapy was given for 14 days. The fourth OKT3 dose was 5 mg in all patients, and the next OKT3 doses were adapted in the following way from POD 3 onwards:

1. If serum OKT3 was above 1000 ng/ml, the next morning dose was 5 mg.
2. If serum OKT3 was between 800 and 1000 ng/ml, the next morning dose was 10 mg.
3. If serum OKT3 was below 800 ng/ml, the patient received a second 5-mg OKT3 injection on the evening of that day, and the next morning dose was 10 mg.

Additional immunosuppression consisted of azathioprine (2 mg/kg per day, tapered to 1 mg/kg per day on POD 14) and steroids. The first and second OKT3 injections were preceded by a methylprednisolone bolus (8 and 4 mg/kg, respectively), prednisone being given starting on POD 2 (0.3 mg/kg per day, tapered to a maintenance dose of 0.17 mg/kg per day after 3 months). Cyclosporin A was introduced on POD 11 and was adjusted to maintain whole blood trough levels (as measured by the specific Sandoz radioimmunoassay) between 150 and 250 ng/ml.

Acute rejection

Acute rejection was diagnosed when serum creatinine rose or failed to decrease as expected in a recently transplanted patient without evidence of other causes of allograft dysfunction. Graft biopsies were performed to confirm the clinical diagnosis in more than 80 % of cases. All rejection episodes were treated with methylprednisolone boluses.

OKT3 monitoring

Trough OKT3 serum levels were measured daily by ELISA, as described by Goldstein et al. [13]. Anti-OKT3 antibodies were also measured by ELISA [13], daily during OKT3 therapy and at weekly intervals for 3 months thereafter.

Quantification of circulating $CD3^+$ cells was done by indirect immunofluorescence using OKT3 mAb and fluoresceinated goat anti-mouse IgG antiserum (Tago, Burlingame, Calif., USA). Briefly, peripheral blood mononuclear cells were isolated from heparinized venous blood by centrifugation through ficoll-hypaque. After reaction with OKT3 followed by the fluoresceinated antiserum, the percentage of $CD3^+$ cells was determined by flow cytometry with a Becton-Dickinson FACS IV analyzer.

Statistical analysis

Statistical differences between groups were estimated using two-tailed unpaired t-tests for numerical variables and using Fischer's exact test for categorical variables.

Results

OKT3 monitoring

Increasing the first three doses of OKT3 to 10 mg (group 2) resulted in higher OKT3 serum levels during the first 4 days of therapy (Fig. 1). Thereafter, the two groups had similar OKT3 serum levels, an expected consequence of the adaptation of OKT3 doses to serum levels. Both groups showed a profound reduction in the the percentage of circulating $CD3^+$ cells, which fell from

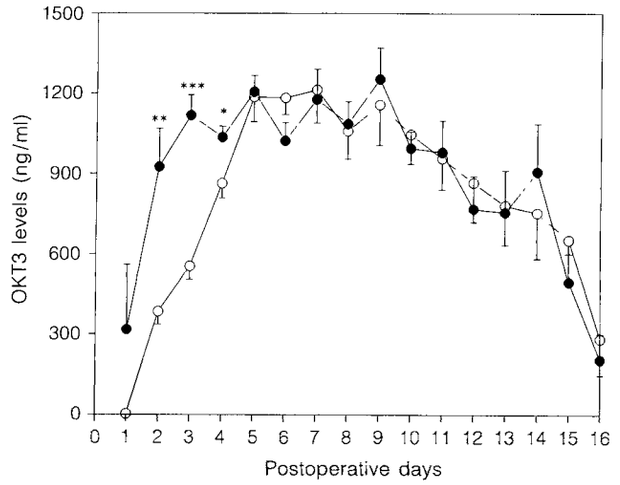

Fig. 1 OKT3 serum levels (mean ± SEM) in group 1 (○; 3 × 5 mg) and group 2 (●; 3 × 10 mg). The three patients from group 1 who did not complete OKT3 therapy are not included. * $P < 0.05$, ** $P < 0.01$; *** $P < 0.001$

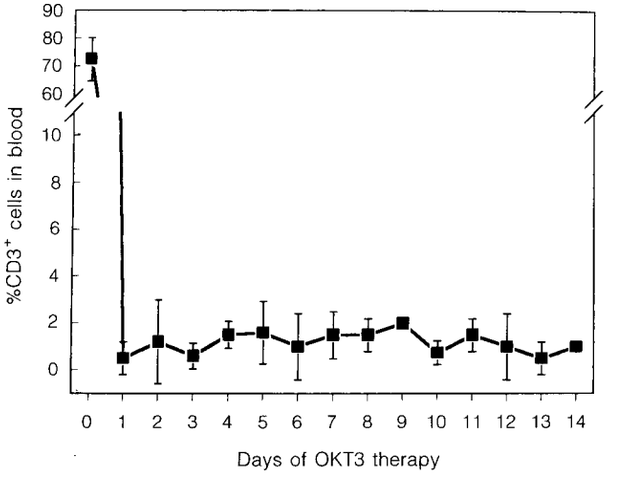

Fig. 2 Percentages (mean ± SEM) of circulating $CD3^+$ cells during OKT3 therapy in pooled group 1 and 2 patients

72.6 % ± 2.3 % (mean ± SEM for combined group 1 and 2 patients; $n = 11$) before therapy to 1.1 % ± 0.2 % (mean ± SEM of 23 samples in 16 patients) during the 1st week and to 1.2 % ± 0.2 % (mean ± SEM of 17 samples in 13 patients) during the 2nd week of OKT3 administration (Fig. 2). The cumulative OKT3 dose in the patients who completed the OKT3 course ($n = 26$) was similar in both groups (mean ± SEM 98 ± 2 mg in group 1 vs 102 ± 3 mg in group 2). All of these patients required increased OKT3 doses to sustain the 1000 ng/ml target OKT3 serum levels. The number of days that supplemental 5-mg OKT3 doses had to be administered was 5.5 ± 0.4 (mean ± SEM; range 4–9) in group 1 patients versus 3.4 ± 0.7 (range 1–9) days in group 2 patients ($P = 0.014$). Eight of the 26 patients required postoperative dialysis, but this did not alter cumulative OKT3 needs (mean ± SEM 98 ± 3 in dialyzed vs 101 ±3 in nondialyzed patients). No correlation could be found between patient's weight and the cumulative OKT3 dose (Fig. 3).

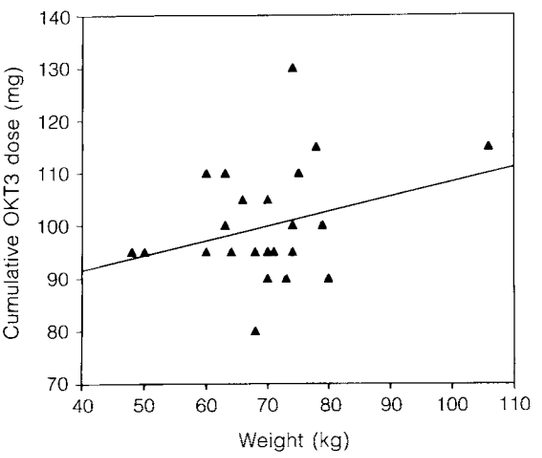

Fig. 3 Cumulative OKT3 dose (mg) according to patient weight. $r = 0.29$

Eight out of the 12 patients from group 1 who completed the OKT3 course and 6 out of the 14 patients from group 2 (14/26 in pooled groups 1 and 2) developed significant anti-OKT3 immunization (IgG titers ≥ 1/1000; P = NS). The 1st day that such high-titered, anti-OKT3 IgG antibodies were detected was similar in both groups (POD, mean ± SEM 16.2 ±2.2, range 11–30 in group 1 versus mean ± SEM 14.8 ± 1.9, range 11–23 in group 2; $P = 0.65$). In 7 of these 14 immunized patients (3 in group 1 and 4 in group 2) this resulted in a sharp drop in OKT3 serum levels during therapy over a 1 to 2-day period. The earliest occurrence of such OKT3 neutralization was on POD 11.

Adverse experiences

OKT3 first-dose reactions (fever, chills, headaches, myalgias, pulmonary and digestive symptoms) were similar in both groups and were of mild intensity. About one-third of group 1 and 2 patients required postoperative dialysis (Table 2). Patient survival was 100 % at 3 months of follow-up. Three patients who received OKT3 at the conventional 5-mg dose (group 1) developed intragraft thrombosis between PODs 1 and 7 (Table 2). No thromboses were observed in group 2. Thrombosis involved either graft artery (patient 1), graft vein (patient 2), or glomerular capillaries (patient 3), presenting in this last case as hemolytic-uremic syndrome. Possible risk factors for thrombosis were found in two cases. Patient 1 had a lupus anticoagulant, and patient 2 had a sequella of a deep venous thrombosis on the iliac vessels used for graft

Table 2 Clinical events during the first 3 postoperative months (P = NS for all parameters)

	Group 1 (3 × 5)	Group 2 (3 × 10)
Patient survival	15/15	14/14
Graft survival	13/15[a]	14/14
Intragraft thromboses	3/15	0/14
Postoperative dialysis	5/15[b]	5/14
Rejection[c]: during OKT3 therapy	0/6.5	0/7
during the first 3 months	2/39	4/42

[a] Two grafts were lost in the 1st postoperative week from main graft vessel thrombosis
[b] Including the two patients with graft failure from thrombosis
[c] Number per patient-month of risk exposure

anastomosis. OKT3 therapy was discontinued after diagnosis of thrombosis in these three patients. The first two grafts had to be removed, while the third was effectively treated by plasmapheresis and high-dose steroids.

Rejections

The incidence of rejection until the end of the 3rd posttransplant month was low and similar in both groups (Table 2). In addition, no patient in either group 1 or 2 experienced rejection during the 14 days of OKT3 therapy. Data from group 1 and 2 were pooled and the incidence of early rejection was compared to that observed in a previous group of patients (n = 66) who received the same immunosuppressive therapy, except that OKT3 was given at a fixed 5-mg dose during the 14 days of therapy. The present protocol allowed for a reduced incidence of early rejections (0/26 in pooled group 1 and 2 patients as compared to 12/66 in historical controls; $P = 0.017$). However, the number of HLA-DR mismatches in pooled group 1 and 2 patients was lower than that in the 66 controls (mean ± SEM 0.07 ±0.05 vs 0.78 ± 0.10; $P < 0.01$), and this might have favored low incidence of rejection in pooled group 1 and 2 patients. Thus, we randomly selected from among the 66 historical controls a group matched for the number of HLA-DR incompatibilities with pooled group 1 and 2 patients. The clinical characteristics of this control group (n = 32) and of pooled group 1 and 2 patients were similar, except for older recipient age and shorter cold ischemia time in pooled group 1 and 2 patients (Table 3). Again, the number of control patients who experienced rejection during the 14 days of OKT3 therapy was significantly higher than that observed in pooled group 1 and 2 patients (6/32 vs 0/26; $P = 0.045$). Data on OKT3 monitoring at rejection in these six control patients (Table 4) showed low OKT3 serum levels in five of them, with four having levels below 500 ng/ml. Rejection occurred early and in the absence of anti-OKT3 antibodies in three cases (patients 1–3). In contrast, rejection occurring during the 2nd postoperative week appeared to be related to the development of anti-OKT3 antibodies (patients 4–6). Five patients had 5 % or fewer circulating $CD3^+$ cells at the time of rejection (Table 4).

Discussion

The first finding from this study was that increasing the dose of a single OKT3 course did not result in additional toxicity. Patient survival was 100 % and no case of lymphoma was observed, confirming previous observations [1]. The intensity of OKT3 first-dose reactions appeared similar with either 5 mg or 10 mg of OKT3 as the initial dose. Thus, the common clinical manifestations [10] were mild in both groups, as has been observed when the first OKT3 injection is given intraoperatively [11]. Postoperative dialysis requirements, indicative of OKT3 nephrotoxicity [30], were similar in both groups. Three patients who received the conventional 5-mg OKT3 induction dose developed intragraft thromboses. This complication is triggered by the procoagulant effects of OKT3 and was first observed after high-dose OKT3 prophylaxis [3]. However, the present study, as well as a review of the thrombotic events that occurred in our institution [4],

Table 3 Characteristics and rejection incidence in patients receiving conventional (5 mg/day) or adapted prophylactic OKT3

	Historical controls	Pooled groups 1 and 2	P
No. of patients	32	29	–
Age (years) of recipients (mean ± SEM)	34.7 ± 1.8	40.6 ± 2.0	0.03
Age (years) of donors (mean ± SEM)	37.7 ± 2.6	33.7 ± 2.4	NS
No. of recipients of first graft	25	26	NS
No. of recipients with anti-HLA immunization	9	5	NS
No. of blood transfusions per recipient (mean ± SEM)	8.06 ± 2.83	4.03 ± 0.79	NS
Cold ischemia time (h; mean ± SEM)	28.9 ± 1.0	24.9 ± 1.3	0.03
Warm ischemia time (min; mean ± SEM)	31.9 ± 1.1	30.9 ± 1.3	NS
HLA antigen incompatibilities (mean ± SEM)			
A	0.75 ± 0.12	0.86 ± 0.16	NS
B	0.97 ± 0.12	0.66 ± 0.11	NS
DR	0.07 ± 0.06	0.07 ± 0.05	NS
No. of rejections during OKT3 administration	6/32	0/26	0.045

Table 4 OKT3 monitoring in patients with rejection during conventional (5 mg/day) OKT3 prophylaxis

Patient	Day of rejection	OKT3 monitoring at rejection		
		Serum levels (ng/ml)	$CD3^+$ cells (%)	Anti-OKT3 IgG
1	4	620	2	–
2	5	220	5	–
3	5	420	1	–
4	11	200	1	1/100
5	13	410	3	1/10000
6	14	Not available	28	1/1000

indicates that the regular 5-mg dose can also precipitate this complication. This is consistent with the biological observations that the first injection of 5 mg OKT3 also induces activation of the coagulation cascade [26, 27]. Our current policy to protect patients from the procoagulant effects of OKT3 is to avoid it in recipients with risk factors for thrombosis, to optimize perioperative volemia, and to administer calcium channel blockers [4]. Preliminary evidence indicates that these measures are sufficient to prevent OKT3-induced thrombosis.

The cumulative OKT3 doses required to maintain serum OKT3 at 1000 ng/ml were about 50 % higher than the 70 mg administered during a 5 mg/day 2-week course. Whether the dose of the initial OKT3 injections is of importance could not be determined in the present study, as results were similar in groups receiving either 5 or 10 mg OKT3 for the first three doses. As the cumulative OKT3 dose and, hence, the cost of therapy were equivalent in both groups, we now routinely give 10 mg OKT3 for the first three injections, based on the assumption that early achievement of elevated OKT3 serum levels might be of additional benefit.

No correlation could be found between patient weight and cumulative OKT3 dose. It could be that the weight dispersion of this series was too small for such a correlation to emerge. On the other hand, the mechanisms of OKT3 clearance are probably complex, involving binding to CD3 receptors as well as to anti-OKT3 antibodies. Whatever the reason, our results do not support the prescription of OKT3 doses based on body weight.

The main conclusion from this study is that close adaptation of OKT3 doses to sustain a 1000 ng/ml OKT3 serum level throughout therapy effectively prevented early graft rejection, which otherwise reportedly occurs in 10 %–20 % of patients [2, 19, 23]. This is probably related to the high amounts of OKT3 necessary to block the function of residual $CD3^+$ cells. While OKT3, even in low doses, induces depletion of $CD3^+$ cells from the circulation and modulation of CD3 T-cell receptors [12], true lymphocyte depletion is short-lived, as T cells with modulated CD3 receptors reappear in the blood after a few days of OKT3 therapy [9, 10]. These T cells display greatly reduced, but still significant, numbers of CD3 T-cell receptors [16, 32]. As only a few T-cell receptors are sufficient to induce T-cell activation [28], optimal immunosuppression during OKT3 therapy probably requires a blockade of these residual receptors. This process is critically dose-dependent, and a 1000 ng/ml OKT3 concentration is required to achieve near-maximal inhibition of T-cell function [8, 25]. The recent description of early rejections in the face of low OKT3 serum levels supports the importance of monitoring OKT3 levels during therapy [14, 18]. Daily determinations of the numbers of circulating $CD3^+$ cells appeared less sensitive in this setting. Indeed, significant numbers of $CD3^+$ cells reappeared in the blood only one to several days after the drop in OKT3 serum levels concomitant to the rejection episode [14, 15, 18].

Recently, several groups have investigated prophylaxis with low-dose OKT3 in kidney transplantation. While these regimens appeared to be effective in decreasing the number of circulating $CD3^+$ cells, OKT3 serum levels were distinctly low in these patients [24]. Nevertheless, kidney transplant recipients treated with low-dose OKT3 had fewer rejections than those receiving CyA-based immunosuppression [24]. Preliminary evidence suggests that the low-dose regiments might prevent early rejection as effectively as the 5 mg/day OKT3 therapy, at least in recipients of a first renal transplant [5, 22]. The main issue is whether the full immunosuppressive effect of OKT3 is already achieved with depletion and modulation of $CD3^+$ cells, allowing for the regular 5 mg/day or even lower doses, or whether it necessitates an additional blockade of residual CD3 molecules, thereby requiring higher OKT3 doses to achieve sufficient serum levels. Our present results suggest that the latter approach is superior in preventing early kidney graft rejection. Whether this will be associated with improved long-term graft survival awaits elucidation.

Acknowledgements This work was supported by Cilag Benelux and by the Fonds de la Recherche Scientifique Médicale (Belgium).

References

1. Abramowicz D, Goldman M, Pauw L de, Doutrelepont JM, Kinnaert P, Vanherweghem J, Vereerstraeten P (1991) OKT3 and post-transplantation lymphoproliferative disorders. N Engl J Med 324: 1438–1439
2. Abramowicz D, Goldman M, Pauw L de, Vanherweghem JL, Kinnaert P, Vereerstraeten P (1992) The long-term effects of prophylactic OKT3 monoclonal antibody in cadaver kidney transplantation – a single-center, prospective, randomized study. Transplantation 54: 433–437
3. Abramowicz D, Pradier O, Marchant A, Florquin S, Pauw L de, Vereerstraeten P, Kinnaert P, Vanherweghem JL, Goldman M (1992) Induction of thromboses within renal grafts by high-dose prophylactic OKT3. Lancet 339: 777–778

4. Abramowicz D, Florquin S, Goldman M (1993) OKT3 nephrotoxicity: from acute tubular necrosis to hemolytic-uremic syndrome. In: Benett WP, De Broe ME, Porter GA, Verpooten GA, Clinical nephrotoxins. Kluwer
5. Alloway R, Kotb M, Hathaway DK, Gaber LW, Vera SR, Gaber AO (1993) Results of a prospective, randomized double-blind study comparing standard vs low-dose OKT3 induction therapy. Transplant Proc 25: 550–552
6. Benvenisty AI, Cohen D, Sregall MD, Hardy MA (1990) Improved results using OKT3 as induction immunosuppression in renal allografts recipients with delayed graft function. Transplantation 49: 321–327
7. Cecka JM, Gjertson D, Terasaki PI (1993) Do prophylactic antilymphocyte globulins (ALG and OKT3) improve renal transplant survival in recipient and donor high-risk groups? Transplant Proc 25: 548–549
8. Chang TW, Kung PC, Gingras SP, Goldstein G (1981) Does OKT3 reacts with an antigen-recognition structure on human T cells? Proc Natl Acad Sci USA 78: 1805–1808
9. Chatenoud L, Baudrihaye JM, Kreis H, Goldstein G, Schindler M, Bach JF (1982) Human in vivo antigenic modulation induced by the anti-T cell OKT3 monoclonal antibody. Eur J Immunol 12: 979–982
10. Debure A, Chkoff N, Chatenoud L, Lacombe M, Campos H, Noel LH, Goldstein G, Bach JF, Kreis H (1988) One-month prophylactic use of OKT3 in cadaver kidney transplant recipients. Transplantation 45: 546–553
11. Doutrelepont JM, Abramowicz D, Borre B, Lemoine A, Pauw L de, Kinnaert P, Vereerstraeten P, Vanherweghem JL, Goldman M (1993) Prophylactic OKT3: practical considerations for the prevention of first dose reactions. Transplant Proc 54: 45–46
12. Goldstein G (1987) Overview of the development of orthoclone OKT3: monoclonal antibody for therapeutic use in transplantation. Transplant Proc 19 [Suppl 1]: 1–6
13. Goldstein G, Fucello AJ, Norman DJ, Shield CF, Colvin RB, Cosimi AB (1986) OKT3 monoclonal antibody plasma levels during therapy and the subsequent development of host antibodies to OKT3. Transplantation 42: 507–511
14. Haak HH, Weening JJ, Rischen-Vos J, Daha MR, Es L van, Woude F van der (1989) Acute cellular rejection during effective early prophylactic OKT3 monoclonal antibody treatment after renal transplantation. Transplantation 48: 352–354
15. Hammond EH, Wittwer CT, Greenwood J, Knape WA, Yowell RL, Menlove RL, Craven C, Renlund DG, Bristow MR, DeWitt CW, O'Connell JB (1990) Relationship of OKT3 sensitisation and vascular rejection in cardiac transplant patients receiving OKT3 rejection prophylaxis. Transplantation 50: 776–782
16. Henell KR, Bakke A, Kenny TA, Kimball JA, Barry JM, Norman DJ (1991) Degree of modulation of cell-surface CD3 by anti-lymphocyte therapies. Transplant Proc 23: 1070–1071
17. Kahana L, Narvarte J, Ackerman J, LeFor W, Weinstein S, Wright C, deQuesada A, Baxter J, Shires D (1989) OKT3 prophylaxis versus conventional drug therapy: single-center perspective, part of a multicenter trial. Am J Kidney Dis 14: 5–9
18. McDiarmid SV, Millis M, Terashita G, Ament ME, Busutill R, Terasaki P (1990) Low serum OKT3 level correlate with failure to prevent rejection in orthotopic liver transplant patients. Transplant Proc 22: 1774–1776
19. Millis JM, McDiarmid SV, Hiatt JR, Brems JJ, Colonna JO II, Klein AS, Ashizawa T, Hart J, Lewin K, Goldstein LI, Levy P, Busuttil RW (1989) Randomized prospective trial of OKT3 for early prophylaxis of rejection after liver transplantation. Transplantation 47: 82–88
20. Monaco AP (1989) Renal prophylaxis with orthoclone OKT3 in the United States. Transplant Proc 21: 7–13
21. Norman DJ, Shield CF, Barry J, Benett WM, Henell K, Kimball J, Funell B, Hubert B (1988) Early use of monoclonal antibody in renal transplantation to prevent rejection. Am J Kidney Dis 11: 107–110
22. Norman DJ, Barry JM, Benett WM, Munson JL, Meyer M, Henell K, Kimball J, Hubert B (1991) OKT3 for induction immunosuppression in renal transplantation: a comparative study of high versus low doses. Transplant Proc 23: 1052–1054
23. Norman DJ, Kahana L, Stuart FJ, Thistlethwaite JJ, Shield CF, Monaco A, Dehlinger J, Wu SC, Van HA, Haverty TP (1993) A randomized clinical trial of induction therapy with OKT3 in kidney transplantation. Transplantation 55: 44–50
24. Parlevliet KA, Berge IJM ten, Wilmink JM, Surachno J, Schellekens TA (1993) A prospective clinical trial comparing low dose OKT3 prophylaxis and prednisolone cyclosporine treatment in renal transplant recipients (abstract). Kidney Int 43: 971–972
25. Platsoucas CD, Good RA (1981) Inhibition of cell-mediated cytotoxicity by monoclonal antibodies to human T cell antigens. Proc Natl Acad Sci USA 78: 4500–4504
26. Pradier O, Marchant A, Abramowicz D, Pauw L de, Vereerstraeten P, Kinnaert P, Vanherweghem JL, Capel P, Goldman M (1992) Procoagulant effect of the OKT3 monoclonal antibody: involvement of tumor necrosis factor. Kidney Int 42: 1124–1129
27. Raasveld MH, Hack CE, Berge I ten (1992) Activation of coagulation and fibrinolysis following OKT3 administration to renal transplant recipients: association with distinct mediators. Thromb Haemost 68: 264–267
28. Romani N, Inaba K, Pure E, Crowley M, Witmer-Pack M, Steinman RM (1989) A small number of anti-CD3 molecules on dendritic cells stimulate DNA synthesis in mouse T lymphocytes. J Exp Med 169: 1153–1168
29. Shield CF, Hughes JD, Lemon JA (1988) Prophylactic OKT3 and cadaveric transplantation at a single center. Clin Transplant 2: 190–193
30. Toussaint C, Pauw L de, Vereerstraeten P, Kinnaert P, Abramowicz D, Goldman M (1989) Possible nephrotoxicity of the prophylactic use of OKT3 monoclonal antibody after cadaveric renal transplantation. Transplantation 48: 524–526
31. Vigeral P, Chkoff N, Chatenoud L, Campos H, Lacombe M, Droz D, Goldstein G, Kreis H, Bach J (1986) Prophylactic use of OKT3 monoclonal antibody in cadaver recipients: utilisation of OKT3 as sole immunosuppressive agent. Transplantation 41: 730–733
32. Woodle ES, Thistlethwaite JR, Jolliffe K, Fucello AJ, Stuart FP, Bluestone JA (1991) Anti-CD3 monoclonal antibody therapy: an approach toward optimalization by in vitro analysis of new anti-CD3 antibodies. Transplantation 52: 361–368