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Immediate and long-term results of ATG induction therapy for delayed graft function compared to conventional therapy for immediate graft function

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Abstract The use of polyclonal antibodies for delayed graft function (DGF) was tested in 83 renal allograft recipients. Conventional immunosuppression (CI) was given to 52 patients with immediate graft function (IGF) while 31 patients with DGF received the polyclonal antibody ATG. Administration of OKT3 was restricted to steroid-resistant acute rejections in both groups. The incidence and severity of acute rejections, graft survival rate, CMV infections, and lymphocyte subsets were examined. ATG patients experienced a total of 0.6 acute rejections per patient, whereas CI patients had 0.9 on the average ($P < 0.05$). Second and third acute rejections occurred less frequently and later in the ATG group than in the CI group ($P < 0.01$). Steroid-resistant acute rejections occurred in 20 of the CI patients (38%) but in only 7 of ATG patients (23%). One-year graft survival in the CI and ATG groups was 98.1% and 93.2%, respectively. A decreased CD4 + to CD8 + T-lymphocyte ratio of about 0.5 was still detectable 5 years after the initial ATG administration. Hence, patients with DGF appear to benefit from induction therapy with ATG.

Key words ATG, delayed graft function, kidney transplantation · Delayed graft function, ATG, kidney transplantation · Induction therapy, ATG

Introduction

Polyclonal antibodies such as antithymocyte globulin (ATG) and monoclonal antibodies such as OKT3 are widely used in clinical transplantation to treat acute rejections, to circumvent cyclosporin (CyA)-induced nephrotoxicity, and to improve long-term allograft survival by delaying the first episodes of acute rejection [6, 20, 21, 24]. In some centers, treatment with ATG or OKT3 is started at the time of grafting as induction therapy [1, 3, 12, 20, 27]. In other protocols, their use is limited to patients with preformed cytotoxic antibodies, second grafts, delayed graft function (DGF), prolonged periods of cold ischemia (CIP), or steroid-resistant rejection episodes [2, 24, 26].

In the Marburg Transplant Center, the immunosuppressive protocol was changed when the murine anti-CD3 antibody OKT3 became available in 1986 in addition to the rabbit polyclonal antibody ATG. OKT3 was shown to be a very potent therapeutic agent, effective even in ATG-resistant acute allograft rejection [20]. However, its use is accompanied by severe side effects

in some cases [11, 20, 24]. Therefore, OKT3 has been restricted to rescue therapy, whereas ATG is administered to recipients with DGF.

In this prospective study, patients with immediate graft function (IGF) received the conventional immunosuppression protocol of steroids and CyA (CI group), whereas those with DGF were immediately given steroids and ATG (ATG group). The administration of OKT3 was limited to rescue treatment of biopsy-proven, steroid-resistant acute rejection episodes in both groups. Two aspects of these induction protocols were investigated. First, we compared the results of both protocols in terms of the incidence of rejections, the amount of OKT3 in steroid-resistant rejection, patient mortality, and 1- to 5-year graft survival. Second, we studied the impact of ATG and OKT3 on changes in lymphocyte subsets, on the rate of occurrence of idiotypic and isotypic antibodies against ATG and OKT3, and on the severity of CMV infections. Finally, we considered whether extending ATG administration to all recipients, regardless of their postoperative graft function should be recommended or not.

Patients and methods

Patients

All adult recipients of a first cadaveric renal allograft who had undergone transplantation between 1 November 1987 and 31 October 1990 were included in the study. Children were not considered since the selection criteria for kidney transplantation in children differ from those in adults.

Therapy

On the day of transplantation, all patients received 5 mg/kg/per day of CyA i.v. (Sandimmun, Novartis, Basel, Switzerland) and 80 mg/day of methylprednisolone i.v. (Urbason, Hoechst, Frankfurt, Germany) just before grafting.

In the case of IGF, conventional immunosuppressive therapy was continued with CyA (8 mg/kg/per day, orally tapered according to whole blood trough levels between 200 and 250 ng/ml during the first 3 months and between 120 and 180 ng/ml thereafter) and 40 mg of methylprednisolone (Urbason) on days 1–3. Starting on the 4th postoperative day, 20 mg of prednisolone (Decortin H, Merck, Darmstadt, Germany) was given; this was tapered after 3 months from 17.5 to 2.5 mg/day for the next 36 months, when it was withdrawn in three patients based on previous experience [16].

In the case of DGF (urinary output < 25 ml/h, C_{creat} < 3.0 ml/min within the first 12 h postoperatively), CyA was replaced with ATG (ATG-Fresenius, Bad Homburg, Germany, 2.5–5.0 mg/kg/per day i.v.). In addition, 0.5–2.0 mg/kg/per day of azathioprine (Imurek, Glaxo-Wellcome, Burgwedel, Germany) was administered, depending on the white blood cell (WBC) counts and C_{creat}. When graft function recovered (C_{creat} > 3.0 ml/min, urinary output > 2000 ml/24 h), CyA was reinstituted with an overlap of ATG and azathioprine for 2–3 days (ATG group).

Acute rejection episodes were assumed when rising serum creatinine levels or levels that did not decline, which could not otherwise be explained, responded to antirejection therapy. They were treated with steroid pulse therapy (prednisolone 500 mg/day i.v. on the 1st day and 250 mg/day on the 2nd and 3rd days, respectively). The monoclonal antibody OKT3 (Cilag, Sulzbach, Germany) was administered for steroid-resistant acute rejection episodes. Steroid resistance was defined as either no response after 3 days of steroid pulse therapy or the third episode of acute rejection in the same patient. In contrast to the steroid-sensitive rejection processes, each steroid-resistant rejection was confirmed by biopsy.

The dosage of OKT3, as well as that of ATG, was adjusted to absolute numbers of lymphocytes (target level < 150 cells/μl) and of T cells (target level < 50 cells/μl). OKT3 administration was stopped when graft function recovered (urine volume > 2000 ml/day, C_{creat} > 3.0 ml/min) or after 3 weeks at the latest, regardless of graft function.

CMV hyperimmunoglobulin preparations were administered prophylactically to CMV IgG-negative recipients regardless of the donor's CMV status and to all recipients who were treated with antilymphocyte antibodies.

Study design

In the first part of the study, both groups of patients were tested for the number of mismatches (MM) on the HLA -A, -B, and -DR loci, for duration of cold ischemia (CIP) and second warm ischemia (WIP), and for the frequency of first, second, and third acute rejection episodes. In both groups, the incidence of steroid-resistant acute rejections with the subsequent institution of OKT3 was recorded, as was the duration and cumulative dosage of OKT3 and the cumulative (methyl-) prednisolone dosage administered in pulse therapy. Finally, the actuarial graft survival rate of all 83 patients at 1, 2, and 5 years and the 6-month mortality after transplantation were determined.

In the second part of the study, the patients were subdivided into three groups according to the exclusive administration of either ATG, OKT3, or CI. Patients who were treated with both ATG and OKT3 (e.g., for steroid-resistant acute rejection after ATG therapy) were not considered in this part of the study. The three groups of recipients were analyzed with regard to the incidence and severity of CMV infections. With a special CMV severity score, five different criteria were considered: (1) CMV serology (positive IgM and/or a fourfold increase in IgG), (2) CMV DNA detection by PCR in serum and/or urine, (3) clinical chemistry (transaminases, lactate dehydrogenase, alkaline phosphatase, leukopenia, and total serum IgM), (4) other herpesvirus infections, and (5) clinical symptoms (e.g., thrombosis, keratoconjunctivitis sicca, pneumonia). When there were positive findings for each item, a maximum score of 12.25 could be attained.

In addition, the ratio of peripheral blood CD4 + to CD8 + T lymphocytes was assessed every 6 months by two-color flow cytometry (Simultest Immune Monitoring Kit, Becton Dickinson, Heidelberg, Germany) during the follow-up period of more than 5 years.

In all recipients who were treated with antilymphocyte preparations, the rate of occurrence of idiotypic and isotypic antibodies during the first 8 weeks was tested using the ELISA technique.

The study was conducted according to the ethical guidelines outlined by the Transplantation Society and involved no commercial transactions.

Statistical analysis

Descriptive statistics were generated for all treatment groups (median and mean values ± SD). Comparisons between all groups

were calculated either with Student's *t*-test or with the median test (mean and median values between two groups, respectively) or with the Kruskal-Wallis test (mean values between three groups). The statistical program package SAS (Version 6.10, SAS Institute, Cary, N.C., USA) was used for all calculations. Actuarial graft survival was calculated using the life table method [8].

Results

Patient characteristics

A total of 83 adult recipients of first cadaveric renal allografts were subjected to the study protocol. IGF occurred in 52 patients who were maintained on CyA and steroids as induction therapy (CI group). In the remaining 31 patients (representing 37.3% of all transplantations), DGF required the immediate institution of ATG (ATG group). This ATG induction therapy was performed over a period of 9.4 ± 5.1 days (range 7–17 days) post-transplantation. The two groups did not differ with respect to mean age, HLA mismatches, or WIP (Table 1).

Table 1 Patient characteristics and acute rejection episodes [*Age* age at transplantation, *MM* mismatches, *CIP* cold ischemia period, *WIP* warm ischemia period (anastomosis time)]

	CI ($n = 52$)			ATG ($n = 31$)		
	n	$\bar{x}$	SD	*n*	$\bar{x}$	SD
Age (years)		48.9	11.6		48.1	10.9
HLA MM-A[a]		0.6[a]	0.6		0.7[a]	0.7
MM-B[a]		0.6[a]	0.6		0.7[a]	0.6
MM-DR[a]		0.2[a]	0.4		0.3[a]	0.5
CIP (h)		22.2	5.4		23	4.8
WIP (min)		42	16		43	12
1st Rejection	29	10.2[b]	6.6	15	11.9[b]	4.9
2nd Rejection	12	23.1[b]	8	2	37.5[b]	30.4
3rd Rejection	4	41.3[b]	10.7	2	64.5[b]	48.8

[a] Values represent the mean of all recipients for each locus
[b] Mean day of occurrence after transplantation

Acute rejection episodes

Nineteen acute rejection episodes were seen in the ATG group, whereas 45 occurred in the CI group, corresponding to 0.6 and 0.9 rejection episodes per patient, respectively ($P = 0.2$, Student's *t*-test; $P < 0.05$, median test). The first acute rejection was seen on average 10.2 ± 6.6 days after transplantation in the CI group and 11.9 ± 4.9 days after transplantation in the ATG group ($P = 0.3399$, Student's *t*-test; $P = 0.3456$, median test). All but one acute rejection episode in the ATG group occurred after the cessation of ATG administration. No difference was observed in the incidence of first acute rejection episodes that were seen in 29 of 52 patients (56%) and 15 of 31 patients (48%) in the CI and the ATG groups, respectively. In contrast, second and third acute rejection episodes were seen in 16 of 29 patients in the CI group and less frequently in 4 out of 15 patients in the ATG group, corresponding to 55% and 27%, respectively ($P = 0.1521$ Student's *t*-test; $P < 0.05$, median test). Moreover, the second and third rejection episodes in the ATG group occurred later than those in the CI group ($P < 0.01$ Student's *t*-test; $P = 0.6608$, median test; Table 1).

Incidence of steroid-resistant acute rejections and cumulative dosages of immunosuppressive agents

Table 2 shows the incidence of steroid-resistant acute rejection episodes as well as the immunosuppressive drug dosages needed for rescue therapy. Steroid-resistant acute rejections with subsequent institution of OKT3 occurred in 20 of the 52 patients (39%) in the CI group but in only 7 of the 31 patients (23%) who had previously received ATG ($P = 0.1385$ Student's *t*-test; $P = 0.1376$, median test).

Table 2 Incidence of steroid-resistant acute rejection episodes and cumulative dosages of immunosuppressive agents

	CI ($n = 52$)			ATG ($n = 31$)		
	n	$\bar{x}$	SD	*n*	$\bar{x}$	SD
ATG therapy	0			31		
Duration (days)					9.4	5.1
Cum. dose (mg/patient)					2272	1221
OKT3 therapy	20			7		
Duration (days)		12.7	4.9		18.3	12.7
Cum. dose (mg/patient)		63.3	24.7		91.4	63.6
M-Pred	20			7		
Cum. dose (mg/patient)		1959	1787		1805	1778

Since, by definition, no ATG was administered in the CI group, these patients were given a substantially lower total dosage of antilymphocyte preparations (ATG plus OKT3): 63.3 vs 2363.4 mg/patient on the average in the CI and ATG groups, respectively ($P < 0.01$). The cumulative OKT3 dosage per patient and the time required for conversion were slightly higher when steroid-resistant rejections occurred after a preceding course of ATG induction than with CI. The cumulative steroid dosage per patient needed for rescue treatment of all acute rejection episodes did not differ in the two groups.

Graft survival and patient mortality

The data regarding graft survival and 6-month mortality are shown in Table 3. The graft survival rates after

Table 3 Graft survival and patient mortality

	CI ($n = 52$)	ATG ($n = 31$)
Graft survival		
1 year	98.1%	93.2%
2 years	96.1%	93.2%
5 years	89.6%	76.3%
Patient mortality		
6 months (n)	0	1

Table 4 Incidence and severity of CMV infections

	OKT3 ($n = 16$)	ATG ($n = 11$)	CI ($n = 16$)
CMV serostatus			
D + R−	25%	27%	38%
D +/− R +	50%	54%	50%
CMV infection			
Primary[a] or reactivated[b]	75%	72%	69%
Persistent IgM (> 6 months)[c]	25%	27%	13%
Severity score ($\bar{x}$)	4.4	5.7	4.1
Score > 6	41.7%	44.4%	26.7%
Steroid dose (mg/patient)	3614	1265	1284

[a] IgG serocon version or detection of IgM or positive blood/urine polymerase chain reaction
[b] Occurrence of IgM or positive blood/urine polymerase chain reaction
[c] IgM detectable for longer than 6 months

1 year in the CI and ATG groups were 98.1% and 93.2%, respectively. After 2 and 5 years, graft survival in the CI group remained greater than that in the ATG group. The difference between the two groups, however, was not statistically significant at any given time.

Within the first 6 months after transplantation, one patient in the ATG group died, whereas there were no deaths in the CI group.

Development of anti-idiotypic or anti-isotypic antibodies

Antibodies against rabbit (ATG-Fresenius) and murine (OKT3) immunoglobulins were observed in 2 of 51 patients (4%) who received antilymphocyte antibodies. Anti-idiotypic antibodies against OKT3 detected in one patient 10 days after initiation of therapy after a previous course of ATG could have contributed to the delayed therapeutic response to steroid-resistant rejection. It was controlled only after increasing the OKT3 dosage to 15 mg/day. Serum sickness occurred transiently in one patient in the ATG group on the 17th day of its administration, when ATG was discontinued due to improving graft function.

Long-term follow-up

Figure 1 shows the long-term follow-up of patients exclusively using either OKT3 or ATG compared to patients maintained on conventional immunosuppression (CI) only. Seven patients in the ATG group who received OKT3 for rescue treatment and four patients in the CI group who had a third acute rejection (Table 1) and who subsequently received both OKT3 and ATG were not included in this evaluation. After the additional exclusion of patients who refused to participate in the more frequent control examinations, 16, 11, and 16 patients remained for long-term follow-up after OKT3, ATG, or CI, respectively. The observation period began at the time of grafting and ended on 31 December 1995.

Three patients, all in the OKT3 group, had to go back on dialysis because of acute ($n = 1$) and chronic ($n = 2$) allograft rejections. Eight patients died with functioning grafts (one cerebrovascular and four cardiovascular accidents, one pneumonia, one sepsis, and one squamous cell lung tumor) 18–56 months after transplantation. One patient in the OKT3 group and two patients in the CI group were lost to follow-up after moving to another town. None of these differences was statistically significant. At the end of the study period, 15 of the 43 patients had been under observation for longer than 60 months.

Serostatus, incidence, and severity of cytomegalovirus infections

The incidence and severity of CMV infections were compared in these three groups (Table 4). The percentage of CMV IgG-negative recipients who received a CMV IgG-positive kidney and that of CMV IgG-positive recipients who received kidneys from either positive or negative donors was similar in the three groups. The difference from 100% in each group represents the CMV IgG-negative recipients who received grafts from CMV IgG-negative donors.

The percentage of patients who experienced a primary or reactivated CMV infection after transplantation was 75%, 72%, and 69% in the OKT3, ATG, and CI groups, respectively; this did not differ significantly. However, the percentage of CMV-infected patients who had persistent IgM CMV antibodies for longer than 6 months was twice as high in those given anti-lymphocyte antibody preparations as in those on CI. No difference of this percentage was found after the administration of either monoclonal or polyclonal antilymphocyte preparations. The mean severity score of CMV infections was slightly higher in the ATG group than in either the OKT3 or the CI group (P = NS). CMV-infected recipients with a severity score above 6.0 were significantly more frequent in the ATG and OKT3 groups than in the CI group ($P < 0.05$, Kruskal-Wallis test).

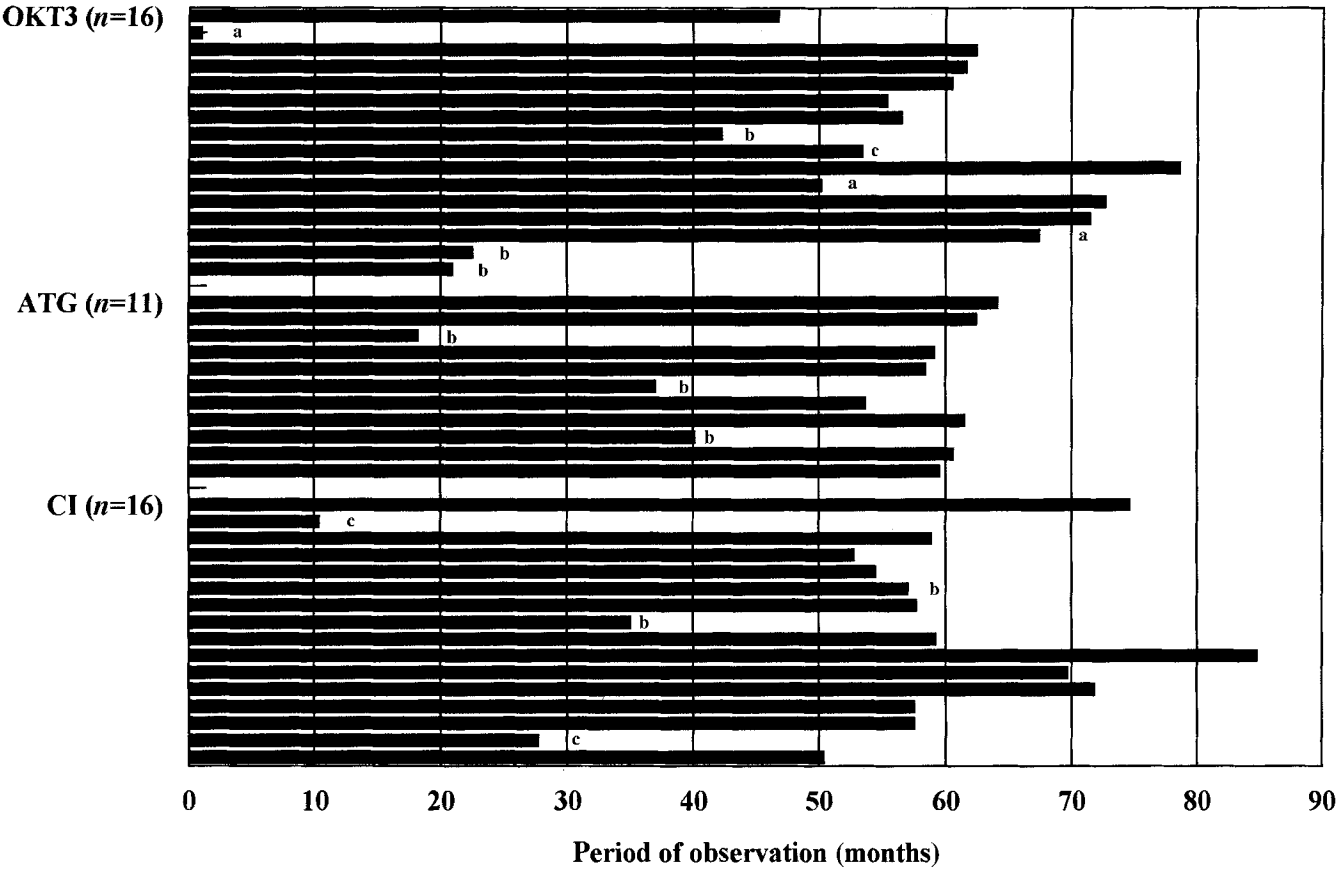

Fig. 1 Long-term follow-up of the patients in the three treatment groups starting on the day of kidney transplantation (*a* dialysis, *b* death, *c* lost to follow-up)

In accordance with the study design, the steroid dosage per patient was highest in the OKT3 group; it diminished markedly in the CI group and was even lower in the ATG group.

Time course in the ratio of CD4 + to CD8 + T cells in the three treatment groups

The ratio of CD3 + CD4 + to CD3 + CD8 + positive T lymphocytes (CD4 + /CD8 + ratio) in all groups under consideration was normal at the time of transplantation (Fig. 2). Upon administration of the antilymphocyte preparations, there was an immediate decrease in both subsets of T lymphocytes to around 100 T cells/μl (data not shown). Six months after transplantation, T cell numbers and the CD4 + /CD8 + ratio in the OKT3 group did not differ significantly from that in the CI group and remained at this level throughout the observation period of 60 months (Fig. 2). In contrast, the CD4 + /CD8 + ratio in the ATG group was 0.5 even at 6 months after transplantation; it remained inverted during the 60 month follow-up and was significantly below that of the OKT3 and CI groups.

Discussion

Up until now, the success of kidney transplantation has been limited due to such problems as acute renal failure, acute renal allograft rejection, chronic rejection, and chronic graft failure. The most favorable results have been achieved with well-matched grafts. Yet, even then, the need for continuous immunosuppressive treatment remains and exposes the recipient to a variety of adverse side effects. Microbial infections and malignancies are among the most serious of these side effects and nephrotoxicity is one of the most frequent events [4, 11]. Many factors must therefore be considered when establishing the most appropriate immunosuppressive therapy.

As early as 1980, ATG was shown to decrease both the incidence of rejection episodes and the mean daily dosage of steroids needed during the first 3 months after kidney transplantation compared to treatment with steroids and azathioprine only [7]. Insufficient therapeutic approaches to viral infections and difficulties monitor-

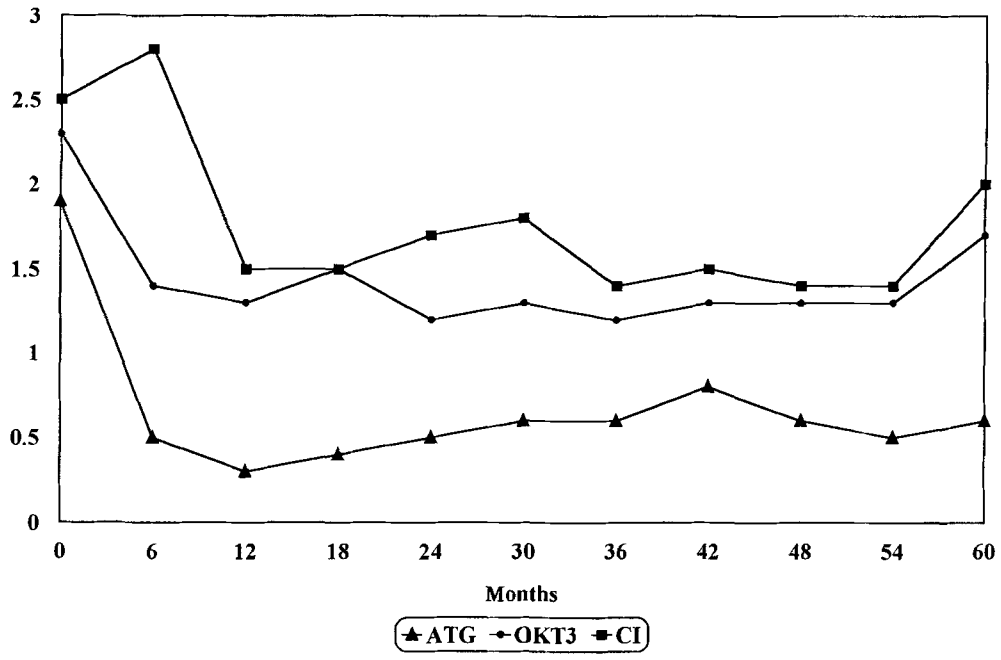

Fig. 2 Ratio of CD4 + to CD8 + T lymphocytes. The CD4 + to CD8 + cell ratios in the ATG group were significantly lower than those in the OKT3 and CI groups throughout the entire postoperative period of observation ($P < 0.001$, Brown-Mood median test). In contrast, the ratios between the OKT3 and CI groups did not differ significantly

ing the ATG dosage prevented its widespread use at that time.

When CyA became available in 1983, the frequency and intensity of acute allograft rejections decreased enormously compared to those after azathioprine and steroid administration. This was accompanied by a 20% improvement in 1-year graft survival in the European multicenter trial [23]. The risk of infectious complications turned out to be far less than that after ATG. Hence, in spite of its nephrotoxicity, CyA became the first-line immunosuppressive induction therapy in the majority of transplant centers worldwide.

Kidneys with DGF are particularly prone to the nephrotoxic effects of CyA, and this condition seems to be associated with more frequent rejection episodes [26] and decreased graft survival [14]. In addition to all of the problems associated with the absence of excretory kidney function and the need for postoperative dialysis treatment, DGF usually requires many, and sometimes hazardous, invasive diagnostics to establish its underlying etiology. Consequently, some transplant centers replaced CyA in primary nonfunctioning grafts with antilymphocyte preparations in order to circumvent additional CyA-induced nephrotoxicity [9, 17].

This policy became more attractive when the murine monoclonal antibody OKT3 became available in 1986. In contrast to the polyclonal antilymphocyte antibody ATG, OKT3 is directed specifically against the epsilon chain of the CD3 complex [15], avoiding the more extensive immunosuppression of ATG with its infectious complications. OKT3 indeed diminished the duration of DGF when compared to a control group with initial nonfunction and maintained on CyA [13]. A comparison of OKT3 with ATG on a randomized basis in 51 recipients with DGF revealed no difference in graft survival [25]. In a similar study of 138 kidney transplant recipients, irrespective of primary graft function, no statistically significant difference was found that could be attributed to the antilymphocyte preparations [9]. This would suggest that the two preparations are equally effective.

Nevertheless, there are two good reasons for not using OKT3 as first choice immunosuppression for primarily non-functioning grafts. The first is the cytokine release syndrome that may subject the transplant recipient to serious clinical conditions [6]. Second, CMV infections appear to be more frequent and more severe after OKT3 than after ATG [3, 11]. Although the immunosuppressive efficacy of OKT3 appears to be superior to that of ATG as rescue treatment [17, 19], it is clinically less well tolerated by the patient and more likely to activate virus replication than polyclonal antilymphocyte preparations [3, 17]. For these reasons, the present study was designed with ATG for induction and with OKT3 only as rescue treatment for steroid-resistant acute rejection either in DGF patients after previous administration of ATG or in IGF patients on CI.

Of the 83 renal allograft recipients who participated in this study, 52 had IGF and could be maintained on CI, whereas 31 had DGF and were given ATG. The 1-year graft survival rate was 93% and 98% for DGF and IGF, respectively (P = NS; Table 3).

Patients in the ATG group had fewer acute rejection episodes than those in the CI group ($P < 0.05$, median

test; Table 1), although hypoxic graft injury appears to be a risk factor of acute rejection [10, 24]. This would seem to indicate the superiority of polyclonal antibodies over conventional immunosuppression, suggesting that ATG administration should be extended prophylactically to all recipients. Yet, the 1-year graft survival rate of 98% in the 52 CI patients raises doubts about any additional benefit that the prophylactic use of antilymphocyte antibodies might have for transplant recipients with IGF. The administration of ATG to all renal allograft recipients in the present study would have subjected an extra 32 patients (52 in the CI group minus 20 in whom OKT3 was instituted, Table 2) to antilymphocyte preparations that were obviously not needed. These patients would not have benefited from the ATG and would presumably only have been burdened by its adverse side effects. Moreover, no one has ever shown prophylactic antilymphocyte antibody therapy to be more beneficial than CyA in a prospective trial in patients with IGF [25].

In another study of 51 patients with DGF who had been given either polyclonal or monoclonal antilymphocyte antibodies, no rejection episodes occurred while the drugs were being administered [17]. This is in line with the mean interval of 2.5 days in our study between the cessation of ATG and the onset of first rejection in 15 of 31 ATG patients, in onle one of whom a rejection episode occurred during ATG administration (Table 1). The protective action of ATG becomes even more evident when the rate of second and third acute rejection episodes are considered. These were less frequent (13% vs 31% with ATG and CI, respectively) and occurred significantly later in the ATG group than in the CI group (Student's t-test $P < 0.01$; Table 1).

Accordingly, the rate of steroid-resistant acute rejections was markedly lower when ATG was administered (23%) than with CI (39%). The number of patients requiring OKT3 for antirejection rescue therapy was, therefore, lower after ATG induction than with CI, and fewer patients in the ATG group were at risk of the adverse side effects of OKT3 (Table 2). These results support the assumed tolerogenic effect of ATG treatment [22]. Seven patients on ATG who experienced steroid-resistant acute rejections nevertheless needed larger amounts of OKT3 and a longer period of time for successful antirejection treatment than 20 patients in the CI group who received OKT3. This observation suggests either that the recipients' immune system "learned the ATG lesson", i.e., to tolerate the graft in attenuating the immune response or that "uneducated" T lymphocytes require an intensified antirejection treatment.

Post-transplant lymphoproliferative disorders, which seem to occur mainly after sequential use of polyclonal and monoclonal antibodies [5, 9], were not seen in any patient in this study.

In the second part of the study, the outcomes of patients who had received either ATG or OKT3 were tested and compared with those of patients maintained exclusively on CI during a maximum follow-up period of 90 months. There was no difference between the groups with regard to graft failure rate, fatalities, or patients lost to follow-up (Fig. 1). Patients who received antilymphocyte preparations had slightly increased and significantly more serious CMV infections than patients on CI. With regard to infectious complications, no significant differences were seen between OKT3 and ATG. These findings are supported by others in patients treated with either OKT3 or Minnesota antilymphocyte globulin (MALG) for delayed graft function [25].

The excessively high steroid dosage in the OKT3 group (there were only patients with steroid-resistant acute rejections in this group; Table 4) might explain why an initially assumed lower impact of OKT3 than of ATG on the antiviral immune response was not reflected in the patients' clinical outcome.

The long-term follow-up data obtained from this part of the study did not reveal any major difference between the administration of ATG and that of OKT3. Except for the diminished CD4 + /CD8 + T-lymphocyte ratio, patient survival, long-term graft failure, and CMV infections were similar on average in both treatment groups during the subsequent 5 years. ATG treatment, starting within 24 h post-transplantation and lasting on the average no longer than 9.4 ± 5.1 days, caused changes in the T-cell subsets that were still detectable after 5 years. However, the pathophysiological consequences of these changes are not yet known [18].

To summarize, the conclusions drawn from the two parts of this study show different aspects of induction therapy with T-cell antibodies. Induction therapy after kidney transplantation with either ATG for DGF or CI for IGF and OKT3 only for steroid-resistant acute rejection yielded favorable results. The long-term results obtained from a subgroup of patients showed an impact of ATG on the CD4 + to CD8 + ratio that was not evident with OKT3.

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