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ORIGINAL ARTICLE

# Long-term results (10 years) of a prospective trial comparing Lo-tact-1 monoclonal antibody and anti-thymocyte globulin induction therapy in kidney transplantation

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## Summary

To evaluate long-term patient and graft survival, and the incidence of acute and chronic rejection, infectious diseases and malignancies following induction therapy with a rat monoclonal interleukin 2 receptor antibody, Lo-Tact-1, or anti-thymocyte globulin (ATG). Forty first-time kidney transplant patients were prospectively randomized to two groups between May 1990 and June 1991. Twenty recipients were treated with Lo-Tact-1 (group 1) and the other 20, with ATG (group 2) during the first 14 days of the transplantation protocol. All patients were treated with azathioprine, steroids and cyclosporin A. Data were collected over 10 years. Median age was 42.1 years in group 1 and 39.3 years in group 2. Six recipients died during the 10 years of follow-up. All had functioning grafts. Death-censored graft survival was 35% in group 1 and 45% in group 2 after 10 years ($P$ = NS). The number of acute rejection was similar in the two groups. Chronic allograft rejection was significantly more frequent in group 2 ($n = 9$) than in group 1 ($n = 3$), $P < 0.05$. Viral and bacterial infections were more frequent in group 2 than in group 1 (respectively 8 vs. 2 and 16 vs. 10, $P < 0.05$). Three patients had cancer. Although both Lo-tact-1 and ATG effectively prevented acute renal rejection, fewer bacterial and viral infections and cases of chronic allograft rejection were observed in Lo-tact-1-treated patients after 10 years of follow-up, demonstrating the potential value of this treatment for kidney transplantation.

## Introduction

In the last 20 years, the end-point of most studies has been the frequency of acute renal rejection (ARR). Recent studies have instead focused on renal function at 6 or 12 months, because of the low frequency of ARR [1]. However, the slope of the graft survival curve after the first years following transplantation has remained similar throughout the 40 years of kidney transplantation, indicating that chronic allograft nephropathy remains a major cause of graft loss and a limiting factor requiring improvement. Therefore, in the absence of validated surrogate markers, studies assessing therapeutic strategies should also evaluate the benefits and problems of therapies in the long-term.

Induction strategies based on depleting or blocking [2] antibodies may have very different impacts on the long-term survival of grafts because they are thought to

affect peripheral acceptance of the graft in different ways. The depletion of T cells with ATG and the inhibition of alloreactive T-cell expansion and, to a lesser extent regulatory T-cell expansion, with anti-IL2R mAb may therefore have different effects on graft outcome and the likelihood of chronic rejection. It has been suggested that anti-IL2R antibodies might reduce the incidence of infectious diseases and cancers [3,4] whereas ATG, by decreasing innate and acquired immunity, is likely to be associated with a much higher frequency of infections and tumors.

Very few studies have evaluated the long-term effects of induction therapies based on anti-IL2R antibodies or ATG in kidney transplantation. The studies that have been carried out have demonstrated that anti-IL2R antibodies are as effective as ATG for preventing ARR in the short term (up to 3 years) following kidney transplantation [3]. Like ATG, anti-IL2R antibodies have been shown to reduce the frequency of acute rejection by >30% with respect to strategies involving no induction in nonimmunized patients [5,6].

The frequency of ARR has been shown to be similar for anti-IL2R and ATG treatments [7,4,8], even in populations at high immunological risk. Anti-rIL2 antibodies were initially developed in rats and mice [9]. Chimeric and humanized anti-IL2 antibodies have since been developed and have similar properties. They inhibit the expansion of T cells, without causing significant T-cell depletion, in the presence of IL-2. Lo-tact-1 is a rat immunoglobulin directed against the 55 kDa-$\alpha$ chain of the IL2 receptor. Its immunological benefits have been demonstrated, primarily in liver [10]. We carried out the first randomized pilot study comparing the efficacy and safety of Lo-tact-1 and ATG for kidney transplantation in 1990 [11]. At 1 year, graft survival and the number of cases of ARR were similar in the two groups, but infectious diseases were less frequent in the group treated with Lo-tact-1 than in the group treated with ATG [11]. We design a new randomized study to describe the outcome with a follow-up of 10 years of adult patients undergoing cadaveric kidney transplantation for the first time. We compared graft survival, and the frequencies of acute rejection, chronic rejection, infectious diseases and cancers between patients treated with Lo-tact-1 and patients treated with ATG, over a 10-year follow-up period.

## Methods and patients

### Trial design

Forty patients receiving kidney transplants between May 1990 and June 1991 were included in a single-center randomized trial. The end-point was long-term graft survival and the effects of ATG and Lo-tact-1 were compared. The secondary end-points were the number of cases of acute cellular and chronic rejection and the frequency of infectious events. Twenty patients were treated with Lo-tact-1, and the other 20, with ATG. All patients aged between 16 and 65 years who received a kidney transplant between May 1990 and June 1991 and from whom informed consent had been obtained were included. Patients were classified as 'low-risk' if they had a panel-reactive antibody score of <50%. Patients who had previously received transplants of any organ or who were receiving antibiotics for severe active infection were excluded. Women of child-bearing age were required to have a negative pregnancy test immediately before entering the study and to practice an approved method of birth control during the study.

Clinical examination, blood count, serum creatine concentration, proteinuria, and whole-blood cyclosporin concentration were determined at each visit. Visits occurred daily during the first month, once per week for 3 months, once per month for 6 months, and then once per year for 10 years.

### Rejection

Cases of acute cellular and chronic rejection were confirmed histologically. Kidney biopsies were carried out if serum creatine concentration increased by 20% of basal levels or if proteinuria exceeded 1 g/day. Acute cellular rejection was defined as interstitial infiltration with mononuclear cells and tubulitis. Chronic rejection and nephrotoxicity because of cyclosporin were analyzed separately. Chronic rejection was characterized histologically by widespread obliterative vasculopathy, glomerulosclerosis and interstitial fibrosis with tubular atrophy [12]. Nephrotoxicity caused by cyclosporin was characterized by hyaline deposits in the artery with or without nephroangiosclerosis, tubular atrophy and scared fibrosis. All kidney specimens were analyzed retrospectively in 2003 and the results were classified according to 97 Banff criteria. Histologically confirmed cases of acute rejection were treated with IV boluses of methylprednisolone for 6 days (10 mg/kg on day 1, then 5, 4, 3, 2 and 1 mg/kg on the following days) in both groups. Steroid-resistant acute rejection was treated with 5 mg/day anti-CD3 monoclonal antibodies (OKT3®, Ortho Biotech, Bridgewater, NJ, USA) administered IV for 7 days.

### Treatment protocol

All patients received a quadruple sequential immunosuppressive regimen. Twenty patients were treated with

10 mg/day Lo-tact-1 IV and the other 20, with 15 mg/day ATG (Thymoglobuline MERIEUX®, Thymoglobuline, Merieux, Lyon, France) for the first 14 days after transplantation. Lo-tact-1 was developed at the Experimental Immunology Unit of the University of Louvain Medical School, Brussels, Belgium. It was produced *in vivo* from the ascitic fluids of LOU/C IgK1b-OKA rats. The antibody was purified using controlled procedures to ensure a high level of purity and the absence of potentially harmful contaminants. The other immunosuppressive drugs administered included corticosteroids: a single bolus of 2 mg/kg methylprednisolone on day 0, then oral prednisone (0.5 mg/kg/day) from day 1 to day 14, followed by a gradual decrease in the dose of prednisone to a baseline of 10 mg/day 1 month after transplantation. Cyclosporin A was administered IV on day 0 (4 mg/kg), then orally at a dose of 8 mg/kg. The dose was subsequently adjusted according to whole-blood concentration and clinical events, if episodes of acute nephrotoxicity occurred. Whole-blood concentrations of cyclosporin were between 400 and 800 ng/ml during the first 6 months, approximately 150–200 ng/ml at 6 months, and approximately 50–100 ng/ml 5 years after transplantation. Azathioprine was introduced on day 45, at an initial dose of 1 mg/kg/day, this dose being decreased when white blood cell counts fell below 4000/mm$^3$. All patients received prophylactic antibiotics: 2 g/day ampicillin, 2 g/day oxacillin and 1 mg/kg/day gentamycin on the day of the kidney transplant and again two days after transplantation, and 400 mg/day sulfamethoxazole–trimethoprime for the first month after kidney transplantation.

### Randomization and statistical analysis

Patients were allocated to the different treatment using a randomization table. ATG was written on 20 pieces of paper and Lo-tact-1, on another 20. These pieces of paper were placed, randomly, in 40 envelopes, numbered 1–40, which were then sealed. Patients were assigned a randomization number (1–40) according to their order of inclusion. The treatment given was that marked in the envelope numbered with the patient's randomization number.

### Statistical analysis

Actuarial graft an patients survival were calculated by the Kaplan–Meier method and compared by log-rank tests. We used chi-squared tests and Student's *t*-tests for other comparisons, as appropriate. We used ANOVA test to compare serum creatinine level and whole cyclosporine trough concentration.

## Results

### Patients

Forty patients were randomly allocated to Lo-tact-1 ($n = 20$) or ATG ($n = 20$) treatment groups. The baseline characteristics of the patients are presented in Table 1; for the treatment groups displayed no clinically relevant differences in mean age, sex ratio, mean HLA-antigen mismatches, mean cold ischemia time, serological test results for cytomegalovirus (CMV), mean time on dialysis and frequency of pregraft panel-reactive antibodies (16.3% vs. 11.2%). In all cases, the frequency of pregraft panel antibodies was <50%. The causes of renal failure were: glomerulonephritis ($n = 14$), tubular interstitial nephritis ($n = 9$), vascular nephropathy ($n = 4$), polycystic kidney ($n = 2$), diabetes ($n = 4$), undetermined ($n = 7$). One patient had cancer before kidney transplantation (cutaneous epidermoid carcinoma) but was considered in remission since 5 years.

### Graft and patient survival

Six (15%) patients died, three of whom died within 3 years of transplantation. Five of the deaths were in the Lo-tact-1 group, with one death in the ATG group. The causes of death in the Lo-tact-1 group were intestinal perforation ($n = 1$), heart failure because of cardiac ischemia ($n = 1$), cutaneous epidermoid carcinoma ($n = 1$), obstructive respiratory insufficiency ($n = 1$) and unknown ($n = 1$). The cause of death was unknown for the only patient who died in the ATG group ($n = 1$). There was no statistically significant difference between the two groups (Fig. 1; Lo-tact-1, $n = 5$, ATG, $n = 1$, $P = 0.18$).

Graft loss occurred in 16 (40%) patients during the 10-year follow-up period [$n = 7$ (35%) in group 1 and $n = 9$ (45%) in group 2, odds ratio = 0.27, CI95% (0.65–

**Table 1.** Demographic and baseline characteristics of patients (ITT).

| | Lo-tact-1 [$n = 20$ (SD)] | ATG [$n = 20$ (SD)] |
|---|---|---|
| Mean age of recipients (year) | 42.1 (12.4) | 39.3 (11.3) |
| Mean time on dialysis (month) | 48.4 (38.6) | 33.7 (22.7) |
| Sex | | |
| Male | 13 | 10 |
| Female | 7 | 10 |
| Mean HLA A/B mismatches | 2.4 (0.2) | 2.7 (0.2) |
| Mean HLA DR mismatches | 1.05 (0.2) | 1.2 (0.1) |
| Mean cold ischemia time (h) | 36.8 (7.4) | 34.5 (7.1) |
| IgG against CMV | 13 | 15 |
| Anti-HLA antibodies (%) | 16.3 | 11.2 |

CMV, cytomegalovirus; HLA, human leukocyte antigen; ITT, intent to treat; SD, standard deviation.

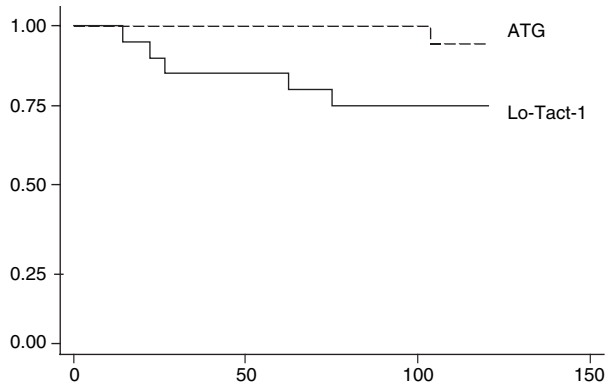


**Figure 1** Kaplan–Meier patient survival for Lo-tact-1 treated ($n = 20$) versus ATG-treated patient ($n = 20$). Comparison with log-rank test $P = 0.18$.

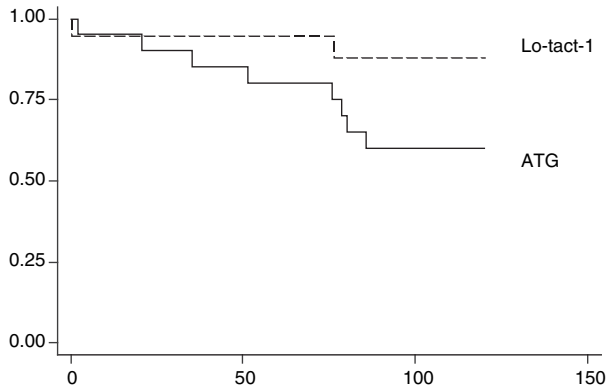


**Figure 2** Kaplan–Meier graft survival for Lo-tact-1 treated patients ($n = 20$) versus ATG-treated patients ($n = 20$) death-censored. Comparison with log-rank test $P = 0.15$.

48.43), $P = 0.1$]. The graft survival rate at 2 years was 87.5%, with no difference between the groups (Fig. 2). The rate of death-censored graft loss tended to be lower in group 1 than in group 2 (Fig. 2). The causes of graft loss were chronic rejection in eight cases (Lo-Tact-1 $n = 1$, ATG $n = 7$), and thrombosis of the graft artery in two cases (Lo-tact-1 $n = 1$, ATG $n = 1$). Serum creatinine concentration was similar in the two groups throughout the study (Fig. 3). Mean serum creatinine concentration was 155.1 μmol/l (±44.4) at 1 year, 167.2 μmol/l at 5 years (±63.1) and 149.7 μmol/l (±56.1) at 10 years, with no statistical difference between the two groups (Table 2).

### Acute rejection, chronic rejection, and nephrotoxicity caused by cyclosporin

The number of patients with at least one acute rejection event was similar in the two groups ($n = 10$ vs. $n = 9$, $P = 0.752$). Only one case of acute rejection was corticosteroid resistant and was treated with OKT3. All the other cases of acute rejection were successfully treated with steroids. There were significantly fewer cases of chronic graft rejection in the group treated with Lo-tact-1 than in the group treated with ATG ($n = 3$ vs. $n = 9$, $P = 0.038$; Table 3). Six patients suffered nephrotoxicity resulting from cyclosporin ($n = 4$ in the Lo-tact-1 group, $n = 2$ in the ATG group, $P = 0.66$). The whole cyclosporine through (Table 2) and the posology of cyclosporine were similar in the two groups.

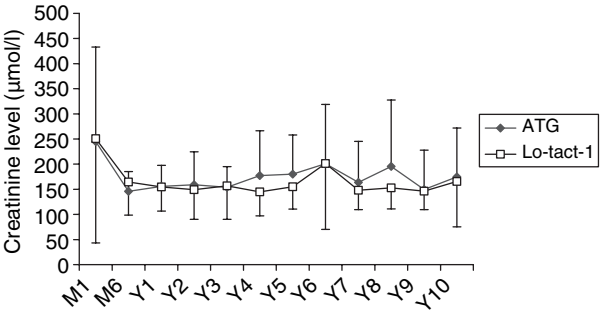


**Figure 3** Mean serum creatinine during the 10-years post-transplant in Lo-tact-1 (open squares) versus ATG treated patients (filled circles) ($P$ = ns). M, months; Y, years.

**Table 2.** Follow-up of creatinine level and whole cyclosporin through during 10 years.

| | Creatinine level plasma | | Whole cyclosporine through | |
|---|---|---|---|---|
| Years | Lo-tact-1 | ATG | Lo-tact-1 | ATG |
| 1 | 154.1 (44.4) | 155.6 (42.0) | 598.6 (291.3) | 547.9 (339.8) |
| 2 | 154.4 (61.7) | 159.1 (65.4) | 446.8 (220.2) | 481.8 (234.9) |
| 3 | 155.3 (53.9) | 153.8 (41.3) | 331.9 (182.6) | 313.2 (213.9) |
| 4 | 161.5 (72.8) | 177.1 (89.1) | 183.0 (119.4) | 186.1 (96.6) |
| 5 | 167.2 (63.1) | 180.1 (77.9) | 156.73 (59.4) | 215.8 (173.9) |
| 6 | 201.1 (121.7) | 201.0 (117.8) | 137.9 (55.2) | 143.6 (53.4) |
| 7 | 155.3 (61.0) | 163.7 (81.4) | 135.6 (60.9) | 141.8 (68.5) |
| 8 | 171.9 (93.5) | 195.3 (132.2) | 95.7 (38.8) | 126.6 (49.70) |
| 9 | 147.7 (55.2) | 149.5 (78.3) | 95.0 (29.3) | 97.1 (25.1) |
| 10 | 149.7 (56.1) | 151.3 (73.7) | 94.3 (27.9) | 96.2 (23.6) |

SD, standard deviation. Comparison with anova test, $P$ = NS.

**Table 3.** Acute and chronic rejection in the two groups.

| | Lo-tact-1 (*n*) | ATG (*n*) | *P*-value |
|---|---|---|---|
| Acute rejection | 9 | 10 | NS |
| Chronic rejection | 3 | 9 | 0.038 |
| Calcineurin inhibitor nephrotoxicity | 4 | 2 | NS |

*n*, number of rejection; NS, nonsignificant.

### Infectious complications

Viral infections (including cytomegalovirus, herpes virus and zoster virus) were more frequent in the ATG group than in the Lo-tact-1 group ($n = 8$ vs. $n = 2$, $P = 0.028$; Table 3). There were five cytomegalovirus infections ($n = 1$ in the Lo-tact-1 group, $n = 4$ in the ATG group, $P = 0.34$), and four herpes virus infections responsible of labial herpes ($n = 1$ in the Lo-tact-1 group, $n = 3$ in the ATG group, $P = 0.60$). There were two zoster virus infections ($n = 2$ in the ATG group and $n = 0$ in the Lo-tact-1 group, $P = 0.49$; Table 4). The zoster virus infections were ophthalmic and lumbar zona. The number of viral hepatitis infection in each group (hepatitis C virus: $n = 2$ for Lo-tact-1, $n = 2$ for ATG; hepatitis B virus: $n = 1$ for Lo-tact-1 and 0 for ATG) was similar. Bacterial infections were more frequent in the ATG group than in the Lo-tact1 group ($n = 16$ vs. $n = 10$, $P = 0.04$; Table 2). Seventeen episodes of pyelonephritis were noted ($n = 6$ in the Lo-tact-1 group, $n = 11$ in the ATG group, $P = 0.11$; Table 2). The bacteria most frequently isolated were *E. coli* and *Klebsiella*, from urinary infectious. There were 10 cases of pneumonia ($n = 5$ in the Lo-tact-1 group, $n = 5$ in the ATG group, $P = 1$) and four cases of septicemia ($n = 0$ in the Lo-tact-1 group, $n = 4$ in the ATG group, $P = 0.11$). There were seven airway infections ($n = 4$ in the ATG group, $n = 3$ in the Lo-tact-1 group, $P =$ NS).

### Malignant complications

Three patients developed cancers. Within the Lo-tact-1 group, one patient developed spinocellular epithelioma in the hand, with several metastases, and another developed cervical carcinoma. In the ATG group, one patient developed cutaneous lymphoma.

**Table 4.** Profile of infections during the 10 years post-transplantation period.

| Infectious diseases | Lo-tact-1 [($n = 20$) $n$ (%)] | ATG [($n = 20$) $n$ (%)] | $P$-value |
|---|---|---|---|
| *Viral diseases** | 2 | 8 | 0.028 |
| Cytomegalovirus | 1 (5) | 4 (20) | NS |
| Herpes virus | 1 (5) | 3 (15) | NS |
| Zoster virus | 0 | 2 | NS |
| *Bacterial diseases*†* | 10 | 16 | 0.047 |
| Pyelonephritis | 6 (30) | 11 (55) | NS |
| Pneumonia | 5 (25) | 5 (25) | NS |
| Septicaemia | 0 | 4 (20) | NS |
| Airway infections‡ | 3 (15) | 4 (20) | NS |

Data are expressed as $n$ (%). NS, nonsignificant.

*Viral disease include infectious diseases caused by cytomegalovirus and/or herpes virus and/or zoster virus.

†Bacterial diseases include pyelonephritis, pneumonia, septicaemia and airways infectious.

‡Airways infections include otitis, tonsillitis and rhinopharyngitis.

## Discussion

This study is the first to evaluate the long-term (10 years) effects of two induction strategies in kidney transplantation. This study was designed in 1990, and we compared the gold standard immunosuppressive regimen for kidney transplantation at that time (ATG, cyclosporin, azathioprine, steroids) with a new regimen (Lo-tact-1, cyclosporin, azathioprine, steroids). We did not analyze specially early events, such as ARR and early graft survival, but we focused on the long-term effects of these induction treatments.

The prevention of acute rejection was an important issue in the 1990s, but the development of new drugs such as FK506, Cell cept, Sirolimus, FTY 720, everolimus and MNA and the use of combined strategies have reduced the rate of acute rejection to <10% in some studies [1]. This makes it difficult to use ARR as the endpoint in studies comparing new and existing protocols, unless large numbers of patients are enrolled. Several studies have also demonstrated that combinations of drugs that decrease ARR significantly may also strongly decrease renal function because of toxicity. Furthermore, the slope of graft survival curves after the first years following transplantation has not changed in 30 years, indicating the persistence of chronic renal dysfunction despite changes in treatment. We therefore investigated long-term complications of kidney transplantation after two different induction strategies, focusing in particular on chronic renal dysfunction, infectious diseases and cancers.

Mortality rates were 5% at 2 years and 15% at 10 years, with no significant difference between the groups (Fig. 1) or from published results [13]. Cardiovascular diseases are the main cause of death following kidney transplantation [14]. In this study, only one patient died from cardiovascular disease, with another patient dying from chronic respiratory disease. However, the causes of death were not directly related to immunosuppressive regimen. Only one death was because of septic shock on diverticulitis, with death occurring suddenly and unexpectedly in most other cases.

The incidence of cancer was low 10 years after transplantation (7% $n = 3$), and similar to that reported by large registries [13,15,16]. One patient died because of a relapse of epidermal carcinoma after transplantation. This tumor had been for 5 years before transplantation.

Graft survival rate was similar in the two groups: 89% at 1 year and 60% at 10 years. The mains causes of graft loss were death and allograft nephropathy. All the patients

who died had a functional graft, a common situation in transplantation. In a population-based survival analysis of 86 562 adults undergoing transplantation between 1987 and 1998, 38% of the 18 482 deaths occurred in patients with a functioning graft, with death accounting for 42.5% of all graft losses [15] Chronic allograft nephropathy is the leading cause of death-censored late graft failure [17] and may be due to several factors such as hypertension, dyslipidemia, diabetes mellitus, acute rejection, chronic graft rejection or calcineurin inhibitor toxicity. The difference between chronic rejection and chronic calcineurin inhibitor toxicity are often difficult to make. However, chronic rejection has been classically described as widespread obliterative vasculopathy and chronic calcineurin inhibitor toxicity as hyaline deposits in the artery with or without nephroangiosclerosis, interstitial fibrosis and tubular atrophy. These pathological changes remain frequent in this modern era of kidney transplantation, detected in approximately 67% of biopsies carried out 2 years after transplantation in a series of 96 recipients of cadaveric kidney transplants treated with tacrolimus or cyclosporin [18]. The control of chronic nephropathy represents a major challenge in improving long-term graft survival. In this study, we carefully differentiated lesions because of calcineurin inhibitor nephrotoxicity from lesions corresponding to chronic rejection, by examining kidney biopsy samples. Chronic rejection was less frequent in the Lo-tact-1 group than in with the ATG group ($n = 3$ in the Lo-tact-1 group, $n = 9$ in the ATG group, $P = 0.038$). The frequency of acute rejection was high (43.2%) in our study, but consistent with that observed in other studies with similar inclusion periods, ranging from 30% to 50% [2,21–23]. Improvements in the monitoring of immunosuppresive regimens and the development of new drugs have since reduced the frequency of acute rejection to roughly 20% during the first 6 months [1]. The number of acute rejection episodes was similar for the Lo-tac-1 and ATG groups ($n = 9$ in the Lo-tact-1 group, $n = 10$ in the ATG group, $P > 0.05$). Other studies, using other anti-IL2R antibodies have reported similar rates of ARR for patients with prior immunization [3].

Viral infections occurred in 20% ($n = 10$) of patients and bacterial infections, in 65% ($n = 26$). CMV was the most frequent viral infection [8] and pyelonephritis was the main bacterial infection observed, as reported in previous studies [4]. Significantly fewer viral or bacterial infectious diseases were observed in the Lo-tact-1 group than in with the ATG group. The frequency of CMV was lower in the Lo-tact-1 than in the ATG group, but this difference was not statistically significant ($n = 1$ in the Lo-tact-1 group, $n = 4$ in the ATG group, $P = 0.34$). Several other studies have reported a lower frequency of infectious diseases with anti-IL2R antibodies (basiliximab and daclizumab) than with ATG [8] although this difference was not significantly different. Anti-IL2R antibodies, unlike ATG, have a specific immunosuppressive effect. They specifically bind to and block the CD25 antigen on the surface of activated T lymphocytes [24] without causing lymphocyte depletion. This may account for the lower frequency of infectious diseases with anti-IL2R treatment than with ATG treatment.

Lo-tact-1 is a rat IgG2b immunoglobulin produced in the Lou/C rat that is used to treat humans [25,26]. Rat IgG2b induces hemolysis and ADCC because it binds human C1q [25,27]. Although similar mechanisms operate with humanized or chimeric anti-RIL2 antibodies, rat anti-IL2R antibodies provide a means of optimizing effector functions and reducing immunogenicity. Lo-tact-1 was as well tolerated as ATG during the induction period of kidney transplantation [11] Unlike ATG, Lo-tact-1 did not cause profound lymphopenia [11]. Lo-tact-1 prevented acute rejection as effectively as ATG in kidney transplantation and OKT3 in liver transplantation [10].

In conclusion, we report here a prospective randomized study comparing ATG with Lotact-1 with a long-term follow-up of 10 years. There were less chronic rejection and infectious diseases in group treated with Lotact-1, but the interpretation of these results must take in account of small number of the cohort.

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