# Ten-Year Follow-Up of Recipients of a Kidney or Heart Transplant Who Received Induction Therapy with a Monoclonal Antibody Against the Interleukin-2 Receptor

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***Objectives:*** **Twelve years ago, we performed two randomized clinical trials to investigate safety and efficacy of induction therapy with BT563, a highly potent murine monoclonal antibody against the interleukin-2 receptor after kidney and heart transplantation. We analyzed the long-term safety and efficacy data from all 120 patients who participated in the two randomized trials after kidney and heart transplantation 10 years ago.**

***Materials and Methods:*** **One of these two trials was a randomized, double-blind, placebo-controlled trial, with 60 primary and secondary kidney allograft recipients (cadaveric and living-related donors). The control group was treated with the standard regimen at that time, consisting of cyclosporin and prednisone. In the study group, BT563 was added for 10 days. The second trial was a randomized, double-blind trial, with 60 recipients of a primary heart transplant. In that study, we compared induction therapy with BT563 with the standard regimen at that time, consisting of cyclosporin, prednisone, and OKT3 (both induction agents were given for 7 days).**

***Results:*** **Patient survival in the kidney trial was excellent: in the BT563 group, 24 patients were alive (80%), and in the placebo, group 21 (70%) 10 years after transplantation. Also, graft survival was good: in the BT563 group, 63.3% of the kidneys (19/30) were functioning, in the placebo group, 72.4% (21/29) were functioning (P = 0.455). Also, in the heart study, patient (and graft) survival was excellent: 18 patients were alive in the BT563 group (58%), and in the OKT3 group, 21 (72%) patients were alive (P = ns). No increase in the incidence of malignancies was observed between patients treated with BT563 compared with the control groups. Patients following heart transplantation more often suffered from a malignancy than did patients after kidney transplantation (20/60 vs 10/59).**

***Conclusions:*** **We report follow-up data on all patients participating in the two randomized trials, and our data reflect a total of 932 years of patient follow-up. Patient and graft survival appear to be excellent in both the BT563-treated patients and the control groups. BT563 treatment was not associated with an increased likelihood of developing infections or malignancies.**

**Keywords:** *BT563, Anti-IL-2R monoclonal antibodies, Long-term follow-up, Transplantation, Malignancies, Infections*

Twelve years ago, we performed two randomized clinical trials to investigate safety and efficacy of induction therapy with a highly potent monoclonal antibody against the interleukin-2 receptor (BT563) after kidney and heart transplantation. BT563 is a murine $IgG_1$ antibody, directed against the α-chain of the IL-2R [1]. Its potency was confirmed in in vitro studies comparing the inhibitory efficacy of several monoclonal antibodies directed against the interleukin-2 receptor (IL-2R) in mixed lymphocyte reaction (MLR) assays [2].

In the first randomized trial, 30 recipients of a primary or secondary kidney allograft received BT563 for 10 consecutive days in addition to standard immunosuppressive therapy after transplantation, consisting at that time of cyclosporin and prednisone. In this study, the control group (30 patients) was treated with cyclosporin, prednisone, and a placebo (double-blind). The first-year results of this

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study were published in 1995 [3]. Patients treated with the monoclonal antibody experienced significantly less acute rejection episodes within the first year following transplantation, whereas its use was not associated with an increased incidence of infectious complications or malignancies. The mean follow-up, however, for patients at publication was short (1 year).

In the second study, in heart transplant patients, 60 patients were randomized either for treatment with cyclosporin, prednisone, and BT563; or for the control group, treated with cyclosporin, prednisone, and OKT3 [4]. In contrast to the trial in kidney allograft recipients, we were unable to show a reduction of the incidence of acute rejection with BT563 compared with OKT3-induction therapy, which was our standard regimen after heart transplantation at that time. Patients treated with BT563 were found to have more early acute rejection episodes, although freedom from acute rejection at 3 months following transplantation was comparable between both groups. Patients with BT563 induction therapy were free from the cytokine release syndrome associated with the use of OKT3.

Since then, monoclonal antibodies against the IL-2R have been further developed. An important next step was the generation of chimeric (basiliximab) or humanized (daclizumab) versions of this class of antibodies. Both daclizumab and basiliximab were proven to be effective in the prevention of acute rejection after kidney transplantation [5-8] and after cardiac transplantation [9]. Long-term safety data of such studies are not available [10]. This information, however, is very important because of the potential risk for the development of malignancies or opportunistic infections even long after transplantation. Death with a functioning graft is one of the major causes of late allograft loss [11]. Potentially, the benefit of using additional immunosuppressive drugs associated with a decreased incidence of acute rejection early after transplantation may be lost if such agents result in more long-term side effects of over-immunosuppression. Therefore, we decided to retrieve long-term safety and efficacy data from all 120 patients who participated in the two randomized trials after kidney and heart transplantation we performed years ago.

## Methods

***Study design.*** The current study analyzed the 10-year outcome of induction therapy with a monoclonal antibody directed against the interleukin-2 receptor α-chain, in two parallel clinical trials designed to assess the safety and efficacy of this antibody after transplantation. One of these two trials was a randomized, double-blind, placebo-controlled trial, with 60 primary and secondary kidney allograft recipients (cadaveric and living-related donors) [3]. Our standard immunosuppressive protocol in kidney transplant patients at that time consisted of cyclosporin and prednisone. The control group was treated with this standard regimen; in the study group, BT563 was added for 10 days. The second trial was a randomized, double-blind trial, with 60 recipients of a primary heart transplant. In the heart transplant study, we compared induction therapy with BT563 with the standard regimen at that time, consisting of cyclosporin, prednisone, and OKT3 (both induction agents were given for 7 days) [4]. For the details of the study design of these two clinical trials as well as for the first-year results, we refer to the publications in 1995 [3] and 1996 [4]. In June 2002, we reviewed all our patients' files since transplantation, collecting all data with regard to the incidence of malignancies, infections, and other safety items appearing after the first year posttransplantation. For malignancies, we reported all cases, also those that occurred within the first year after transplantation.

***Patients.*** The demographics for BT563-, placebo-, and OKT3-treated patients were described in the original publications [3,4]. Follow-up was available for all kidney and heart transplant recipients (total n = 120), except for one kidney recipient, of whom we know is alive, but unfortunately no follow-up data are available. Data from all other 119 patients were collected up to the last outpatient visit or death. Of these 119 patients, we here present the 10-year follow-up results. As not all patients survived for the entire 10 years, we have collected not 119 x 10 = 1190 years of follow-up, but 932 years.

***Study drug.*** BT563 was a murine antibody of the $IgG_1$-kappa isotype, directed against the α-chain of the IL-2Receptor complex. It was developed and produced by Wijdenes in Besancon and was previously known as B-B10 [12]. Later it was produced by Biotest Pharma, Dreiech, Germany.

## Results

### Kidney

***Patients.*** A total of 60 patients who received a kidney

allograft were enrolled into the prospective randomized trial between March 1992 and August 1993: 30 patients were assigned to the BT563 group and 30 to the placebo group. One patient in the placebo group was lost to follow-up. The two groups were similar with respect to age, sex, race, cause of end-stage renal disease, and type of donor (cadaveric/living related) [3].

***Patient and graft survival.*** Patient survival was excellent: after a mean follow-up of 7.8 years (range: 5 weeks to 10.0 years) in the BT563 group, 24 patients were alive (80%), and in the placebo group 21 (72.4%) (Figure 1A). The main cause of death was cardiovascular disease (n = 8). In two patients, the cause of death was a malignancy (Table 1). Also, graft survival was good: in the BT563 group, 63.3% of the kidneys (19/30) were functioning, in the placebo group, 72.4% (21/29) were functioning ($P$ = 0.455) (Figure 1B). Of the patients with a failed graft, 10 patients had been re-transplanted.

***Malignancies.*** In the BT563 group, 7 patients developed a malignancy (23%). Six patients developed one malignancy and 1 patient suffered from 3 malignancies (Figure 2). In the placebo group, 3 patients (10%) developed a malignancy, in all cases these were nonmelanoma skin malignancies. From the 7 patients in the BT563 group, 4 delevoped a nonmelanoma skin malignancy, 1 patient suffered from a posttransplant lymphoproliferative disease (PTLD), 1 patient was diagnosed with having acute myeloid leukemia, stomach, and skin cancer (these malignancies, however, did not all appear at the same time), 1 patient suffered from lung cancer, and 1 patient had an oropharyngeal carcinoma (Table 2).

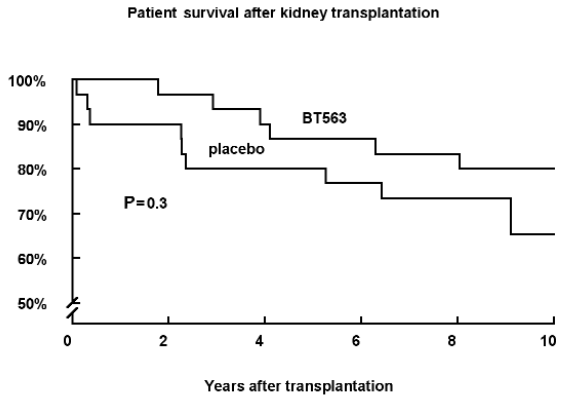


**Figure 1A.** Patient survival following kidney transplantation. Patients were treated with BT563 induction therapy or placebo, combined with cyclosporine and corticosteroids.

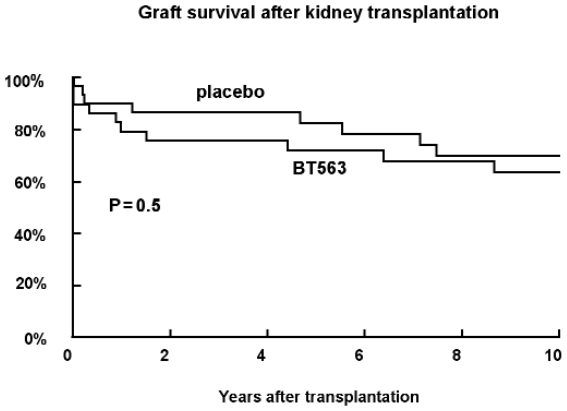


**Figure 1B.** Graft survival following kidney transplantation.

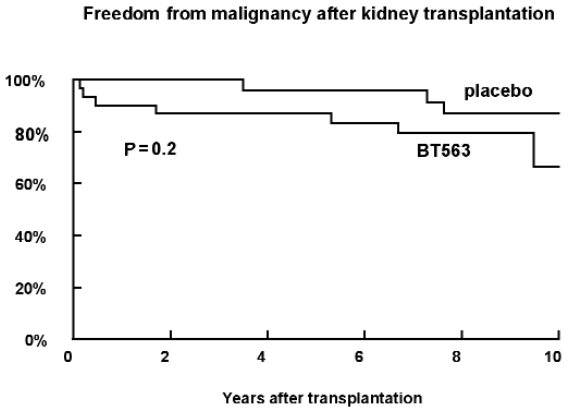


**Figure 2.** Freedom from malignancy following kidney transplantation. Patients were treated with BT563 induction therapy or placebo, combined with cyclosporine and corticosteroids.

**Table 1.** Causes of death after kidney or heart transplantation

| | Kidney | | Heart | | |
|---|---|---|---|---|---|
| | BT563 | placebo | BT563 | OKT3 | **Total** |
| No. of patients | n = 30 | n = 29 | n = 31 | n = 29 | N = 119 |
| Cardiac failure | 3 | 5 | 4 | 3 | 15 |
| Infection | 1 | 1 | 1 | 0 | 3 |
| Malignancy | 2 | 0 | 3 | 3 | 8 |
| Cerebrovascular | 0 | 0 | 2 | 1 | 3 |
| MOF* | 0 | 0 | 2 | 0 | 2 |
| Other | 0 | 1 | 1 | 0 | 2 |
| Unknown | 0 | 1 | 0 | 1 | 2 |
| **Total** | 6 | 8 | 13 | 8 | 35 |

*__MOF__ = Multiple organ failure

**Table 2.** Malignancies occurring after kidney or heart transplantation (mean follow-up = 7,8 years, range: 5 weeks -10,0 years for kidney transplantation and mean follow-up = 7,7 years, range: 0–10,3 years for heart transplantation).

| | Kidney | | Heart | | |
|---|---|---|---|---|---|
| | BT563 | placebo | BT563 | OKT3 | **Total** |
| No. of patients | n = 30 | n = 29 | n = 31 | n = 29 | N = 119 |
| Lymphoma (incl. PTLD) | 1 | 0 | 1 | 3 | 5 |
| Lung | 1 | 0 | 2 | 2 | 5 |
| Stomach | 1 | 0 | 0 | 0 | 1 |
| Kidney | 0 | 0 | 0 | 1 | 1 |
| Skin | 4 | 3 | 5 | 3 | 15 |
| Other | 2 | 0 | 1 | 2 | 5 |
| **Total** | 9 | 3 | 9 | 11 | 32 |

***Infections.*** In this study, we focused our attention on infections which appeared after the first postoperative year, and for which a hospital admission was necessary. For data relating to the first posttransplant year, we refer to the original publication [3]. In the BT563 group, 12 patients (12/30) suffered from an infection, all were of bacterial origin (Table 3). Four patients had pneumonia, 1 patient had a sepsis with *Pseudomonas aeruginosa*, 1 patient had a bacterial peritonitis, 2 patients had a bacterial infection of the upper respiratory tract, 2 patients had an infection with Enterobacter of the urinary tract, 1 patient had a gastroenteritis with *Shigella*, and 1 patient had a pharyngitis (Table 4). In the placebo group, 12 patients (12/29) had a total of 15 infections: 9 infections were bacterial (9/15), 5 were of viral origin (5/15), and 1 was of unknown nature (1/15) (Table 3). For the causative microorganisms, we refer to Table 4.

**Table 3.** Infections requiring hospital admission after first year following kidney or heart transplantation.

| | **Kidney** | | **Heart** | | |
|---|---|---|---|---|---|
| | BT563 | placebo | BT563 | OKT3 | **Total** |
| No. of patients | n = 30 | n = 29 | n = 31 | n = 29 | N = 119 |
| Viral | 0 | 5 | 6 | 3 | 14 |
| Bacterial | 12 | 9 | 13 | 12 | 46 |
| Fungus | 0 | 0 | 0 | 0 | 0 |
| Parasite | 0 | 0 | 1 | 0 | 1 |
| Other | 0 | 1 | 0 | 0 | 1 |
| **Total** | 12 | 15 | 20 | 15 | 62 |

**Table 4.** Subtypes of infections requiring hospital admission after first year following kidney or heart transplantation.

| | **Kidney** | | **Heart** | |
|---|---|---|---|---|
| | BT563 | placebo | BT563 | OKT3 |
| No. of patients | n = 30 | n = 29 | n = 31 | n = 29 |
| **Bact** pneumonia | 4 | 2 | 6 | 4 |
| Sepsis | 1 | 3 | 1 | 0 |
| Urinary tr | 2 | 3 | 0 | 2 |
| Upper resp tr | 2 | 0 | 2 | 5 |
| Shigella | 1 | 1 | 0 | 1 |
| Peritonitis | 1 | 0 | 1 | 0 |
| Other | 1 | 0 | 3 | 0 |
| **Viral** Upper resp | 0 | 2 | 3 | 0 |
| Herpes zoster | 0 | 2 | 0 | 2 |
| Gastroenteritis | 0 | 0 | 3 | 1 |
| Unknown | 0 | 1 | 0 | 0 |
| **Other** | 0 | 1 | 1 | 0 |

***Immunosuppressive therapy.*** At the last follow-up visit in the BT563 group, 46.7% (14/30) of the patients were treated with azathioprine and prednisone, 33.3% used cyclosporin and prednisone (10/30), 3.3% mycophenolate mofetil and prednisone (1/30), 3.3% tacrolimus and prednisone (1/30), and in 13.3%, information on the current immunosuppressive medication was unavailable (4/30). In the placebo group, 37.9% used azathioprine and prednisone (11/29), 51.7% used cyclosporin and prednisone (15/29), 6.9% mycophenolate mofetil and prednisone (2/29), and in 3.5%, the current medication was unknown (1/29).

**Heart**

***Patients.*** In the heart transplantation study, 60 patients were randomly allocated to either the BT563 (31 patients) or the OKT3 (29 patients) induction therapy. These two groups were similar with respect to age, sex, race, and cause of end-stage cardiac disease [4].

***Patient and graft survival.*** Also in the heart study, patient (and graft) survival was excellent: after a mean follow-up of 7.7 years (range: 0 to 10.3 years), in the BT563 group, 18 patients were alive (58%), and in the OKT3 group, 21 (72%) (Figure 3). The major cause of death was cardiac failure due to graft vascular disease: 4 patients in the BT 563 group, 3 patients in the OKT3 group. Other causes of death were a malignancy (6/60), multiorgan failure (2/60), and cerebrovascular disease (3/60) (Table 3). In the BT563 group, 8 patients (25.8%) developed end-stage renal failure. Four patients needed hemodialysis, and in 4 patients, peritoneal dialysis was started as renal replacement therapy. In the OKT3 group, none of the patients developed end-stage renal failure, although we have identified 3 patients in this group with a serum creatinine above 400 μmol/l, and in whom renal replacement therapy is expected to be necessary soon.

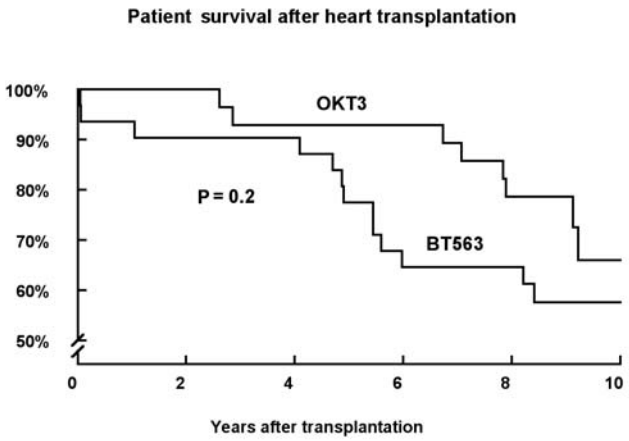


**Figure 3.** Patient survival following heart transplantation. Patients were treated with either BT563 induction therapy or OKT3 induction therapy, combined with cyclosporine and corticosteroids.

***Malignancies.*** In the heart transplant group, 9 patients who had been treated with BT563 (9/31), developed a malignancy. In the OKT3 group, 11 patients (11/29) developed a malignancy. (Table 2; Figure 4). The 9 malignancies in the BT563 group originated from the skin (5/9), from the lung (2/9), a non-Hodgkin lymphoma (1/9), or prostate cancer (1/9).

In the OKT3 group, 3 malignancies originated from the skin (3/11), 2 patients had a lymphoma (2/11), 2 patients suffered from a lung carcinoma (2/11), 1 patient developed a posttransplant lymphoproliferative disease (PTLD) (1/11), 2 patients had prostate cancer (2/11), and another had a renal carcinoma (1/11) (Table 2).

***Infections.*** Similar to the kidney study, we focused our attention on infections which appeared after 1 year posttransplantation and for which hospital admission was necessary (Table 3). In the BT563 group, 16 patients (16/31) had a total of 20 infections: 65% were of bacterial origin (13/20), 30% were viral (6/20), and 1 patient suffered from a *Pneumocystis carinii pneumonia* (1/20). In the OKT3 group, 12 patients (12/29) had a total of 15 infections: 80% were bacterial (12/15), 20% viral (3/15). Most of the infections were of a similar nature, like the infections reported in the kidney transplant recipients. For the causative microorganisms we refer to Table 4.

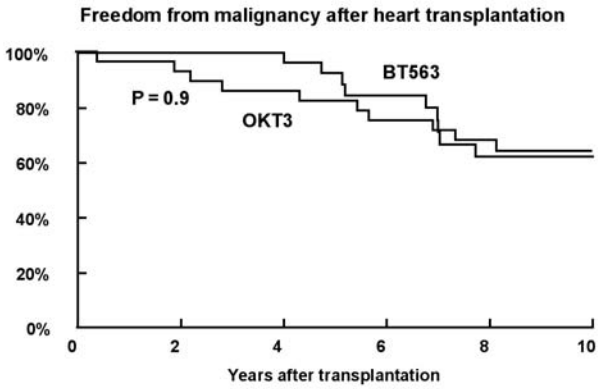


**Figure 4.** Freedom from malignancy following heart transplantation. Patients were treated with either BT563 induction therapy or OKT3 induction therapy, combined with cyclosporine and corticosteroids.

***Immunosuppressive therapy.*** At last follow-up, patients in both the BT563 and the OKT3 group were on either cyclosporin and prednisone therapy (56.7%) or on maintenance treatment with cyclosporin, prednisone, and azathioprine (26.7%). The remainder of the patients was being treated with other combinations, such as tacrolimus and prednisone (11.7%).

***Diabetes mellitus.*** In the BT563 group, 8 patients (8/31) developed de novo diabetes mellitus. In the OKT3 group, this was the case for 5 patients (5/29).

## Discussion

The monoclonal antibody used in our studies (BT563) was a murine antibody directed against the α-chain of the IL-2R (CD25) [13]. At the time we started our studies, the IL-2R seemed to play a crucial role in the development of alloreactivity and in the generation of alloreactive clones of cytotoxic T cells [14,15]. However, given the pleiotropy and redundancy of the cytokine network, it is difficult to intervene in T cell activation. This is highlighted by the structure of the functional high-affinity IL-2R complex, consisting of an α, β, and γ-chain. Several other cytokine receptors have a similar structure, and it is known that the receptors of IL-7, IL-15, and IL-4 share the γ-chain of the IL-2R. Anti-CD25 blocked T cells may still become activated by IL-2 through the IL-2R β and γ-chain, while IL-15 can stimulate through the IL-15R α-chain and the β and γ-chain, all shared by IL-2 and IL-15. We demonstrated that mRNA for the macrophage derived T-cell growth factor IL-15 was abundantly present in rejecting cardiac grafts during anti-IL-2R monoclonal antibody therapy, while at the same time mRNA for IL-2 was absent [16]. To further demonstrate the importance of IL-15 in the activation of lymphocytes during blockade of the IL-2R α-chain, we showed functional responses of these lymphocytes to IL-2 and IL-15 stimulation [17]. Recently Koch et al confirmed our finding that daclizumab not only blocks the α-chain, but also reduces the expression of the IL-2R β-chain [18-20].

Nevertheless, despite these immunologic pathways of bypassing the effect of anti-IL-2R monoclonal antibodies, in our study among kidney transplant recipients, we observed a significant reduction in the incidence of early acute rejection episodes, when combining cyclosporin and prednisone with BT563. In the heart transplant patients, the incidence of acute rejections in the patients treated with BT563 was comparable to those in the OKT3-treated control group. BT563 was a murine antibody, and the majority of patients developed human-anti-mouse antibodies (HAMA response), limiting the half-life of the antibody and therefore its efficacy [21]. As a next step, daclizumab, a molecularly engineered human $IgG_1$ antibody incorporating the antigen-binding regions of the parent murine antibody and basilix-

imab, a chimeric anti-IL-2R monoclonal antibody were developed. Both monoclonal antibodies are not immunogenic, no sensitization is observed, their half life is > 20 days, and after two intravenous gifts of daclizumab in peripheral blood, no free IL-2 receptor (IL-2R) α-chain (CD25) binding sites are found for up to 2 months after transplantation [22]. Long-term follow-up data with the use of these antibodies are scarce. Niemeyer et al recently reported their 4-year follow-up data of a cohort of 28 liver transplant patients treated with daclizumab induction [23]. In this study, no increased incidence of opportunistic infections and no cases of posttransplant lymphoproliferative disease were observed. Bumgardner et al published the 3-year follow-up data of 126 daclizumab-treated patients, and compared the incidence of adverse sequelae such as serious infections and posttransplant lymphoproliferative disease with a placebo-treated control group (134 patients) and found no differences [24].

Our study shows an excellent long-term survival for both the kidney and heart transplant patients. We report follow-up data on all patients participating in the two randomized trials, and our data reflect a total of 932 years of patient follow-up. No increase in the incidence of malignancies was observed between patients treated with BT563 compared with the control groups. We decided also to include the follow-up data of those patients in the kidney study who had lost their allograft and had subsequently been retransplanted. In these patients, we were unable to detect any malignancies. Patients following heart transplantation more often suffered from a malignancy than patients after kidney transplantation (20/60 vs 10/59). This might reflect the higher overall amount of immunosuppressive therapy in heart recipients compared with kidney recipients. Especially, OKT3 has been reported to be associated with an increased incidence of lymphoproliferative disorders in cardiac transplant recipients [25]. Reasons for the higher immunosuppressive load in heart transplants are the use of non-HLA-matched organs and the fear of fatal acute rejection episodes, where in kidney patients the availability of dialysis offers an alternative renal replacement therapy. The incidence of malignancies in both sets of patients is not increased compared with the incidences from large registries [26-28]. The murine BT563 antibody that we used is rapidly neutralized by human anti-mouse antibodies and is unlikely to have a major impact on malignancy incidence against a background of 10 years of daily immunosuppressive therapy. We therefore think the nonsignificant difference in malignancies developing in our renal transplant patients (7 in patients treated with BT563 and 3 in the placebo group) does not refelect a long-term effect of our BT563 induction therapy.

In this study, no data on chronic allograft dysfunction are shown. Although we do search for myocardial ischemia in all patients yearly, we do not have coronary angiograms of all heart transplant patients long after transplantation. Mancini et al found a reduced incidence of graft atherosclerosis in heart transplant patients treated with daclizumab induction therapy [29]. In kidney transplant recipients, we do not perform protocol biopsies.

The high incidence of end-stage renal failure in 8 BT563-treated heart transplant recipients is striking. We were aware that renal failure following heart transplantation is a complication observed in up to 10% of all patients [30,31]. It is usually thought to be related to the long-term use of cyclosporin [32] or tacrolimus [33]. In this study, all cases of renal failure needing renal replacement therapy were in the BT563- treated heart transplant recipients. Pretransplant identification of patients at risk for developing renal failure has proven to be very difficult [31].

In the OKT3 group, however, 3 patients did have renal insufficiency, as reflected by a serum creatinine above 400 μmol/l, and also in these patients, initiation of renal replacement therapy is to be expected within the next 2 years. Again, this high rate of renal failure is probably due to the use of a high-dose immunosuppressive therapy, in this case cyclosporin. After the introduction of drugs like mycophenolate mofetil and sirolimus, we now have the possibility to taper and eventually to avoid cyclosporin therapy after organ transplantation.

For the monitoring of cyclosporin therapy, we have used the strategy of trough blood concentration monitoring over the years. As increasing numbers of reports now show that trough (predose) concentrations do not predict total cyclosporin exposure reliably over a 12-hour dose interval, it is conceivable that in some of the patients developing renal failure, total exposure to the drug was much higher than suspected on the basis of the trough level measurements [34]. Clinical data from controlled studies now show $C_2$ monitoring is a more-relevant guide to cyclosporin dosing than trough concentration monitoring, impacting on the incidence of acute graft rejection in kidney and liver transplantation [35].

Our long-term follow-up data on 932 years of

patient follow-up are reassuring, but we have to keep in mind that the murine antibody we have used has a shorter terminal half life and a shorter biological half life than the currently used anti-IL-2R monoclonal antibodies. Therefore, our results cannot be fully extrapolated to the use of daclizumab and basiliximab.

We have to stimulate both doctors and industry in collecting long-term follow-up data on cohorts of patients such as ours. Long-term follow-up on these therapies will hopefully be presented in the near future.

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