Toxoplasma gondii Serostatus Is Not Associated With Impaired Long-Term Survival after Heart Transplantation

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Background. Conflicting data have been reported about the effect of Toxoplasma serostatus on mortality after heart transplantation. Either a positive or a negative recipient Toxoplasma serostatus was found to be associated with increased mortality.

Methods. We evaluated the effects of T. gondii infection on survival of our 582 cardiac allograft recipients operated upon between June 1984 and July 2011.

Results. The 258 Toxoplasma seronegative and 324 seropositive recipients differed in age, pretransplantation diagnosis, ischemia time, renal function, donor Toxoplasma serology, and maintenance immunosuppression. After a median follow-up time of 8.3 years (range, 0–26 years), 117 (45%) seronegative and 219 (67%) seropositive patients died. No difference was found in deaths due to cardiac allograft vasculopathy. After adjustment for all relevant clinical characteristics, the recipient Toxoplasma serostatus was not associated with mortality (hazard ratio, 1.21; 95% confidence interval [CI], 0.95–1.54). With the Toxoplasma serostatus combination donor negative/recipient negative as a reference, univariate hazard ratios for the Toxoplasma serostatus combinations were D+/R− 0.52 (95% CI, 0.37–0.73), D−/R+ 0.65 (95% CI, 0.40–1.05), and D+/R+ 0.78 (95% CI, 0.57–1.07). Multivariate analysis, however, showed that donor Toxoplasma serostatus was not independently associated with mortality.

Conclusions. The Toxoplasma serostatus of both the recipient and donor appeared not to be independent risk factors for mortality after heart transplantation.

Keywords: Heart transplantation, Toxoplasmosis, Cardiac allograft vasculopathy, Mortality.

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Until now, two studies investigated whether the long-term survival after heart transplantation is affected by the Toxoplasma serostatus of the recipient and the donor (1, 2). These studies, however, yielded conflicting results as to the recipient serostatus. Arora et al. reported that a Toxoplasma seropositive status in heart transplant recipients was associated with an increased risk of all-cause mortality as well as risk of death by cardiac allograft vasculopathy and Doesch et al. reported that a Toxoplasma seronegative status was associated with an increased mortality risk (1, 2). In both studies, no association of donor serostatus and mortality was found.

Toxoplasma gondii is an obligate intracellular protozoan parasite with a worldwide distribution that can invade and replicate in almost all nucleated cells of warm-blooded mammals. After the primary acute infection, the parasite remains in the body in a quiescent state by the formation of tissue cysts in predominantly muscle and brain tissue. Therefore, toxoplasmosis is a lifelong infection and the prevalence of human T. gondii infections thus increases with age. Its prevalence is reported to be more than 50% in many parts of the world (3). In immunocompetent individuals, the infection is usually asymptomatic, although cases of severe disease due to unusual T. gondii genotypes from South and Central America have
TABLE 1. Characteristics of all 582 cardiac allograft recipients

| Toxoplasma serostatus | Number of patients, n (%) | P     |
|-----------------------|---------------------------|-------|
| Negative              | 258 (44)                  |       |
| Positive              | 324 (56)                  |       |

Recipient

|           |               |       |
|-----------|---------------|-------|
| Female gender, n (%) | 81 (31) | 61 (19) | 0.0001 |
| Age (years; mean±SD) | 41±16 | 51±10 | <0.0001 |
| <19, n (%)          | 37 (14) | 5 (1.5) | <0.0001 |
| 19–59, n (%)        | 204 (79) | 268 (83) | 0.26 |
| >59, n (%)          | 17 (7) | 51 (16) | 0.0006 |

Pretransplantation diagnosis

|                          |               |       |
|--------------------------|---------------|-------|
| Cardiomyopathy, n (%)    | 142 (55)      | 131 (40) | 0.0006 |
| Ischemic heart disease   | 103 (40)      | 179 (55) | 0.0002 |
| Failure of first graft   | 2             | 3     | NS    |
| Other                    | 11 (4)        | 11 (3) | NS    |
| Prior cardiac surgery    | 67 (26)       | 77 (24) | 0.30 |
| PRA >0 (number of patients) | 76 (31) | 99 (32) | 0.87 |
| Long-term LVAD           | 9 (3)         | 5 (2)  | NS    |
| CMV seronegative         | 121 (47)      | 140 (43) | 0.39 |
| CMV mismatch (D+/R-)     | 58 (22)       | 69 (21) | 0.76 |
| Serum creatinine pre-Tx (L; μmol/L mean±SD) | 110±42 | 125±52 | <0.0001 |
| Diabetes mellitus pre-Tx, n (%) | 17 (6) | 16 (5) | 0.30 |

Donor

|                       |               |       |
|-----------------------|---------------|-------|
| Female gender, n (%)  | 129 (51)      | 144 (44) | 0.17 |
| Age (years; mean±SD)  | 32±14         | 33±13  | 0.48 |
| <51, n (%)            | 230 (91)      | 282 (88) | 0.46 |
| >50, n (%)            | 24 (9)        | 37 (12) | 0.42 |
| Cause of death, n (%) |               |       |
| Trauma                | 94 (41)       | 138 (48) | 0.11 |
| Hemorrhagic stroke    | 116 (51)      | 139 (48) | 0.63 |
| MM AB+DR >4, n (%) of patients | 121 (48) | 167 (52) | 0.26 |
| Toxoplasma seronegative, n (%) | 105 (41) | 85 (26) | 0.003 |
| Toxoplasma serostatus unknown | 29 (11) | 126 (38) | <0.0001 |

Operation

|                        |               |       |
|------------------------|---------------|-------|
| Ischemia time (min; mean±SD) | 180±44 | 171±43 | 0.02 |

Postoperative course

|                     |               |       |
|---------------------|---------------|-------|
| Induction therapy, n (%) | 202 (78) | 244 (76) | 0.52 |

Maintenance immunosuppression, n (%)

|                          |               |       |
|--------------------------|---------------|-------|
| Cyclosporine based        | 117 (48)      | 203 (68) | <0.0001 |
| Tacrolimus based          | 133 (52)      | 99 (32) | <0.0001 |
| +MMF                     | 64 (26)       | 54 (18) | 0.02 |
| Statin started immediately post-Tx | 123 (48) | 123 (38) | 0.05 |

Acute rejection

|                          |               |       |
|--------------------------|---------------|-------|
| 0 episodes, n (%) of patients | 58 (22) | 79 (25) | 0.59 |
| >2 episodes, n (%) of patients | 55 (21) | 82 (25) | 0.26 |
| CMV disease, n (%)        | 33 (14)       | 60 (20) | 0.06 |
| Treatment for hypertension at 1 year | 160 (62) | 228 (70) | 0.09 |
| Diabetes mellitus post-TX | 59 (23)       | 80 (25) | 0.84 |

TABLE 1. (Continued)

| Toxoplasma serostatus | Serum creatinine at 1 year (μmol/L; mean±SD) | P     |
|-----------------------|---------------------------------------------|-------|
| Negative              | 127±66                                     | 145±67 | 0.003 |
| Positive              |                                           |       |

Cholesterol at 1 year (mmol/L; mean±SD)

|                       |               |       |
|-----------------------|---------------|-------|
| Negative              | 6.4±5.5       | 6.4±2.3 | 0.82 |
| Positive              |               |       |

Triglycerides at 1 year (mmol/L; mean±SD)

|                       |               |       |
|-----------------------|---------------|-------|
| Negative              | 3.6±1.4       | 2.3±1.2 | 0.12 |
| Positive              |               |       |

CAV at 1 year n (%) of resp. 230/280 CAG

|                       |               |       |
|-----------------------|---------------|-------|
| Negative              | 19 (8)        | 26 (9)  | 0.75 |
| Positive              |               |       |

CAV at 4 years n (%) of resp. 171/218 CAG

|                       |               |       |
|-----------------------|---------------|-------|
| Negative              | 25 (15)       | 36 (17) | 0.78 |
| Positive              |               |       |

RESULTS

Between June 1984 and July 2011, a total of 582 heart transplants have been performed in 577 patients. Recipients with a retransplant have been assessed as separate cases. Follow-up was complete in all cases. The Toxoplasma serostatus of the 582 cases was determined and Table 1 shows the characteristics of cardiac allograft recipients according to their pretransplantation Toxoplasma serostatus. The 324 Toxoplasma seropositive cases were 10 years older than the 258 seronegative cases, suffered more often from ischemic heart disease, and had worse renal function. Due to missing serum samples, the serostatus of 155 donors was estimated. The serostatus of the 582 cases was determined and Table 1 shows the characteristics of cardiac allograft recipients.
seronegative recipients and 85 (26%) of the *Toxoplasma* seropositive recipients received the heart of a seropositive donor.

The use of induction immunosuppression was not different between *Toxoplasma* seropositive and seronegative cases, but the *Toxoplasma* seropositive recipients received more often cyclosporine instead of tacrolimus for maintenance immunosuppression (Table 1). Early statins were more often administered to *Toxoplasma* seronegative patients. During follow-up, there were no differences in the number of rejection episodes, in the occurrence of cytomegalovirus (CMV) disease, or in treatment of hypertension and diabetes mellitus. The prevalence of cardiac allograft vasculopathy, shown at routine angiography after 1 and 4 years, was similar in both groups.

**Mortality and T. gondii Seropositivity**

During a median follow-up time of 8.3 years (range, 0–26 years) 336 transplant recipients died, of whom 219 (65%) were *Toxoplasma* seropositive and 117 (35%) were *Toxoplasma* seronegative. Long-term cumulative survival of the (unadjusted) *Toxoplasma* seropositive patients appeared worse than that of the *Toxoplasma* seronegative patients (Fig. 1). Causes of death were comparable between the *Toxoplasma* seropositive and seronegative recipients (Table 2). Especially, no difference was found in deaths due to cardiac allograft vasculopathy defined as late cardiac death. (Table 2). This applied to all recipients as well as to the 4-year survivors.

Univariate analysis of all-cause mortality in all 582 cases showed that, besides recipient *Toxoplasma* seropositivity, recipient age, ischemic heart disease, pretransplantation diabetes mellitus, reoperation, pretransplantation and 1-year posttransplantation renal function, and cardiac allograft vasculopathy at 1 and 4 years were risk factors of mortality, whereas tacrolimus (instead of cyclosporine) based immunosuppression and early statins appeared to be protective (Table 3). After adjustment for all relevant clinical characteristics independent of the *P* value, as described in Table 3, the recipient *Toxoplasma* serostatus was not associated with higher mortality (hazard ratio [HR], 1.21; 95% confidence interval [CI], 0.95–1.54; *P*=0.18).

Multivariate analysis of the *Toxoplasma* serostatus combinations shown in Table 3 showed that donor *Toxoplasma* serostatus was not independently associated with mortality (HR [95% CI], D+/R- 0.74 [0.52–1.06], D-/R+ 0.88 [0.53–1.46], and D+/R+ 0.82 [0.56–1.20]). Analysis of the 510 one-year survivors showed that female gender of the recipient was an extra univariate risk factor of mortality (not shown). Multivariate analysis confirmed characteristics as recipient age and cyclosporine-based immunosuppression (vs. tacrolimus) as independent risk factors of mortality and the protective effect of early statins (Table 4). Pretransplantation diabetes mellitus was an independent risk factor in all patients and in the 1-year survivors.

**DISCUSSION**

We showed that the long-term survival of heart transplant recipients is not associated with the *Toxoplasma*

![FIGURE 1. Survival of all recipients according to *Toxoplasma* serostatus.](image-url)
TABLE 3. Univariate predictors of all-cause mortality in all patients

| Predictor                              | HR    | 95% CI       | P      |
|----------------------------------------|-------|--------------|--------|
| **Recipient**                          |       |              |        |
| Female gender                          | 1.174 | 0.897–1.538  | 0.24   |
| Age                                    | 1.027 | 1.017–1.037* | <0.001 |
| Ischemic heart disease                 | 1.528 | 1.230–1.899* | <0.001 |
| PRA > 0                                | 1.184 | 0.948–1.480  | 0.147  |
| CMV seropositive                       | 1.174 | 0.946–1.459  | 0.15   |
| CMV mismatch (D+/R−)                   | 0.833 | 0.635–1.094  | 0.19   |
| **Toxoplasma**                         |       |              |        |
| CMV seropositive                       | 1.496 | 1.193–1.875* | <0.001 |
| Serum creatinine pre-Tx                | 1.002 | 1.000–1.004* | 0.03   |
| Diabetes mellitus pre-Tx               | 1.216 | 1.024–1.444* | 0.03   |
| **Donor**                              |       |              |        |
| Female gender                          | 1.001 | 0.806–1.245  | 0.99   |
| Age                                    | 1.006 | 0.996–1.015  | 0.25   |
| Trauma cause of death                  | 1.078 | 0.851–1.364  | 0.53   |
| MM AB+DR > 4                           | 1.025 | 0.827–1.270  | 0.82   |
| **Donorrecipient Toxoplasma serostatus combinations** |       |              |        |
| Donorrecipient negative/negative (reference) | 1.00 |       |        |
| Donorrecipient positive/negative       | 0.524 | 0.037–0.73  | <0.001 |
| Donorrecipient negative/positive       | 0.65  | 0.40–1.05   | 0.08   |
| Donorrecipient positive/positive       | 0.78  | 0.57–1.07   | 0.12   |
| **Operation**                          |       |              |        |
| Reoperation                            | 1.224 | 1.022–1.466* | 0.03   |
| Ischemia time                          | 1.000 | 0.998–1.003  | 0.75   |
| **Postoperative course**               |       |              |        |
| Induction therapy                      | 0.942 | 0.757–1.173 | 0.59   |
| Maintenance immunosuppression          |       |              |        |
| Cyclosporine based                     | 2.830 | 2.111–3.794* | <0.001 |
| Tacrolimus based                       | 0.353 | 0.264–0.474* | <0.001 |
| Early statin per protocol              | 0.485 | 0.367–0.640* | <0.001 |
| Acute rejection                        |       |              |        |
| Number of episodes 0                   | 0.805 | 0.623–1.041 | 0.10   |
| Number of episodes >2                  | 0.881 | 0.652–1.191 | 0.41   |
| CMV disease                            | 0.989 | 0.738–1.326 | 0.94   |
| Treated hypertension at 1 year post-Tx | 0.672 | 0.530–0.852* | 0.001 |
| Diabetes mellitus post-Tx              | 0.986 | 0.791–1.228 | 0.90   |
| Serum creatinine at 1 year post-Tx     | 1.003 | 1.001–1.004* | <0.001 |
| Total cholesterol at 1 year post-Tx    | 0.937 | 0.884–0.994* | 0.03   |
| Triglycerides at 1 year post-Tx        | 0.923 | 0.838–1.077 | 0.115  |
| CAV at 1 year post-Tx                  | 1.097 | 1.026–1.173* | 0.01   |
| CAV at 4 years post-Tx                 | 1.116 | 1.043–1.194* | 0.002 |

*a Significant difference.

Therefore, an imbalance of beneficial demographics in our Toxoplasma seronegative recipients (younger, less ischemic heart disease, better renal function, more tacrolimus maintenance immunosuppression, and more early statin use) may have masked a true mortality risk. We assume, however, that this has been overcome by putting all known risk factors into the multivariate model.

Searching for an explanation of the contradictory results of the studies of Arora et al. (1) and Doesch et al. (2) and our study, we demonstrated several differences between the studies. A summary is presented in Table 5. Populations differ not only in patient demographics but also in percentages of Toxoplasma seronegative recipients and in percentages of donors with unknown Toxoplasma serostatus. No Toxoplasma prophylactic treatment was used in the study of Arora et al. (1). The most obvious difference, however, is the time period covered by the studies. Time as a confounding factor applies above all to our study, which includes almost the whole history of calcineurin inhibitor–based heart transplantation. Multivariate analysis of all known risk factors will not completely have corrected for this issue. We refrained from adding “era” effect as a risk factor in to the analysis because of too much overlap of the different eras at different time points in diagnostic procedures (for CMV, toxoplasmosis, acute rejection, and cardiac allograft vasculopathy) as well as in therapeutic strategies (CMV prophylaxis, Toxoplasma prophylaxis, induction and maintenance immunosuppression, use of statins, etc.). When we included “year of transplant” as a continuous variable the HR (95% CI) was 0.80 (0.79–0.82) but in the multivariate model, there was large confounding with several other variables such as “early statin,” which was given only after 1995. Therefore, we had to remove “year of transplant” from the model.

Others demonstrated an association of recipient Toxoplasma seropositivity with especially mortality due to cardiac allograft vasculopathy (1). The background of such

TABLE 4. Multivariate predictors of all-cause mortality

| Predictor                              | HR    | 95% CI       | P      |
|----------------------------------------|-------|--------------|--------|
| **All patients**                       |       |              |        |
| Recipient age                          | 1.028 | 1.011–1.046  | 0.001  |
| Diabetes mellitus pretransplantation    | 2.267 | 1.027–5.004  | 0.04   |
| Cyclosporine-based maintenance immunosuppression | 2.564 | 1.611–4.808 | <0.001 |
| Early statin per protocol              | 0.518 | 0.305–0.879  | 0.02   |
| **1-year survivors**                   |       |              |        |
| Recipient age                          | 1.029 | 1.012–1.047  | 0.001  |
| Diabetes mellitus pretransplantation    | 2.344 | 1.061–5.179  | 0.035  |
| Cyclosporine-based maintenance immunosuppression | 2.655 | 1.656–4.255 | <0.001 |
| Early statin per protocol              | 0.488 | 0.283–0.839  | <0.001 |
| **4-year survivors**                   |       |              |        |
| Recipient age                          | 1.037 | 1.011–1.063  | 0.005  |
| Cyclosporine-based maintenance immunosuppression | 2.251 | 1.289–3.930 | 0.004  |
| Early statin per protocol              | 0.319 | 0.143–0.712  | <0.001 |

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serostatus of neither the recipient nor the donor. By inclusion of more patients and a longer follow-up period, our results may partly solve the disagreement between earlier findings (1, 2).

Beneficial effects of the early use of statins and tacrolimus-based maintenance immunosuppression have been reported earlier from the U.S. and European centers (10–13).
The antibiotic prophylactic drugs given to Toxoplasma mismatch recipients (D+/R-) could also have a direct or indirect immunomodulatory effect. Although such a phenomenon has not been reported for pyrimethamine and sulfadiazine, spiramycin induces increased interleukin-6 production by monocytes in vitro (7). In addition, patient outcome could be negatively influenced by side effects of the antibiotic prophylactic drugs. Spiramycin is hepatotoxic, pyrimethamine can induce bone marrow suppression, and sulfadiazine is hepatotoxic and nephrotoxic. However, oral folic acid administration prevents the negative side effects of a pyrimethamine-sulfadiazine regimen in most cases. This study, as well as the studies by Arora et al. (1) and Doesch et al. (2), did not identify a difference in mortality between Toxoplasma seronegative recipients that received the heart of a seropositive versus a seronegative donor, suggesting that the antibiotic prophylactic drugs given to Toxoplasma mismatch recipients (D+/R-) do not negatively affect outcome.

Our analyses confirmed recipient age and pretransplantation diabetes mellitus as independent risk factors for mortality. Our finding that cyclosporine (vs. tacrolimus) for maintenance immunosuppression appeared to be an independent risk factor of all-cause mortality confirms the results of Guethoff et al., who recently showed a survival benefit of tacrolimus versus cyclosporine in the 10-year follow-up of a randomized trial (12). Early prescription of statins had a protective effect as has been demonstrated by others in short-term as well as in long-term studies (10, 11).

In conclusion, we found that neither the Toxoplasma serostatus of the transplant recipient nor the serostatus of the donor is an independent risk factor for mortality after heart transplantation. Time bias, however, may have acted as a confounding factor for our results, but long term studies in a field with frequent changes in diagnostic and therapeutic strategies will always be harmed by the effects of time.

**Limitations of the Study**

Our analysis involved all heart transplant recipients, from the start of the program in 1984. This resulted in a study population that embraced the whole evolution of heart transplantation with increasing recipient and donor ages, different diagnostic laboratory methods, different immunosuppression protocols, and different therapies for infection prophylaxis. In addition, statins early after transplantation were introduced only from 2000. Another limitation is the lack of donor Toxoplasma serostatus in a considerable number of transplant recipients. The larger percentage of unknown donor Toxoplasma serostatus in the seronegative recipients can be explained by the fact that more effort was put in finding out the donor serostatus in seropositive recipients because of the required prophylaxis in case of a mismatch. In this respect, however, it may be important that Toxoplasma seronegative recipients of a donor with unknown serostatus have received the, for that time, usual prophylactic treatment.

**MATERIALS AND METHODS**

**Patients**

From the start of the heart transplant program in 1984, clinical data of all heart transplant recipients have been prospectively collected. Patients consented to use deidentified data for research purposes and the institutional review board of the Erasmus MC approved the present study. Enrolled were all cases who underwent heart transplantation between June 1984 and July 2011. For the study, the database was closed on July 15, 2012.

Patients with preformed donor-specific anti-human leukocyte antigen antibodies (panel-reactive antibody [PRA] 4%) were only transplanted after a negative crossmatch. During the early years of the program, only donors under age 36 were accepted for transplantation. Later on, the upper

| TABLE 5. Comparison between studies on Toxoplasma serostatus and survival after heart transplantation | Arora et al. (1) | Doesch et al. (2) | Current study |
|---|---|---|---|
| Number of patients | 288 | 344 | 582 |
| Recipient age (years, mean) | 54 | 52 | 47 |
| Donor age (years, mean) | 36 | 38 | 32 |
| Toxoplasma seronegative recipients (%) | 73 | 55 | 44 |
| Unknown donor Toxoplasma serology (%) | 15 | ? | 27 |
| CMV mismatch D+/R- (%) | 21 | 23 | 22 |
| Time period of study | 1994–2005 | 1989–2008 | 1984–2012 |
| Inclusion of >1 era | | | |
| For donor age | ? | + | + |
| For diagnostic strategies | | | |
| Toxoplasma serology | − | + | + |
| CMV | ? | ? | ++ |
| AR | − | + | + |
| CAV | − | − | + |
| For therapeutic strategies | | | |
| Toxoplasma prophylaxis | − | + | ++ |
| CMV prophylaxis | ? | ? | ++ |
| CAV (e.g., PCI) | ? | ? | + |
| Induction | ? | ? | + |
| Immunosuppression | | | |
| Maintenance | − | + | + |
| Immunosuppression | | | |
| Early use of statins | + | − | + |

?, no information available; −, only one modification during the study; ±, only one criterion with minor modifications; +, two modifications; ++, more than two modifications.
Immunosuppression and Rejection

Over the years, several regimens of induction therapy have been used, initially within sequential randomized trials: ALG (lymphogobulin; Institut Merieux, Lyon, France), OKT3 (Ortho Pharmaceutical, Raritan, NJ), and BT653 (daclizumab, Zenapax; Roche, Basel, Switzerland) (16–18). Later on, ALG (lymphogobulin) was used, and during recent years, rabbit antithymocyte globulin (ATG; Fresenius, Kabi, The Netherlands) was administered.

From 1984 to 1999, maintenance immunosuppression consisted of cyclosporine and steroids complemented with azathioprine or mycophenolate mofetil (MMF) when two or more rejection episodes had occurred. From 2000 onwards, the regimen consisted of a combination of tacrolimus, steroids, and MMF. Rejection episodes were treated with pulsed high doses of steroids or rabbit ATG (initially rabbit ATG; National Institute for Public Health, Biltboven, The Netherlands and later on with rabbit ATG (Genzyme Polyclonals, Marcy-l’Etoile, France) in cases of steroid-resistant rejection.

From 1984 to 1990, CMV mismatched patients received prophylactic treatment against CMV seropositive donor (or of the heart of a donor of whom the serostatus was not known) according to the knowledge at the time and sequentially consisted of a 6-month course of pyrimethamine was always combined with folinic acid. When the EIA method resulted in equivocal test results, the Toxoplasma serostatus was determined by examination of follow-up sera and/or by Western blot analysis as described before (23).

Infection Prophylaxis

Prophylaxis against T. gondii was applied in Toxoplasma seronegative recipients of the heart of a Toxoplasma seropositive donor (or of the heart of a donor of whom the serostatus was not known) according to the knowledge at the time and sequentially consisted of a 6-month course of spiramycin (1985–1989) or pyrimethamine (1989–1994). From 1995 to 2003, the combination of pyrimethamine and sulfadiazine was used. The administration of pyrimethamine was always combined with folinic acid.

In the early phase of the program, CMV seronegative recipients of the heart of a seropositive donor received passive immunization with anti-CMV immunoglobulins (Cytotect; Biotest Pharma, Dreieich, Germany) during the first 72 days after transplantation (24). Later on, oral valganciclovir was prophylactically administered for 6 months (or longer in case of rejection treatment) in these CMV mismatched patients.

Assessment of Cardiac Allograft Vasculopathy

Annual coronary arteriography was performed during the first 7 years of the program (25). Later on, coronary angiography (CAG) was performed per protocol after 1 year and repeated only after 4 years when no disease other than wall irregularities was shown. From year 5, CAG was performed when annual myocardial perfusion imaging showed perfusion defects or when electrocardiogram changes or other clinical signs of coronary syndromes occurred (26). The use of statins (pravastatin) per protocol early after transplantation was introduced in 1996.

Definitions

The presence of cardiac allograft vasculopathy was defined positive when at least ISHLT-CAV1 was diagnosed by CAG (27). Early cardiac death was defined as death caused by primary graft failure. Late cardiac death was defined as death caused by arrhythmia, conduction disorder, unwitnessed sudden death, or heart failure with angiographically or by postmortem examination-proven allograft vasculopathy.
22. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005; 24: 1710.

23. Sluiters JF, Balk AH, Essed CE, et al. Indirect enzyme-linked immunosorbent assay for immunoglobulin G and four immunosassays for immunoglobulin M to Toxoplasma gondii in a series of heart transplant recipients. J Clin Microbiol 1989; 27: 529.

24. Balk AH, Weimar W, Rothbarth PH, et al. Passive immunization against cytomegalovirus in allograft recipients. The Rotterdam Heart Transplant Program experience. Infection 1993; 21: 195.

25. Balk AH, Simoons ML, vd Linden MJ, et al. Coronary artery disease after heart transplantation: timing of coronary arteriography. J Heart Lung Transplant 1993; 12: 89.

26. Elhendy A, Sozzi FB, van Domburg RT, et al. Accuracy of dobutamine tetrofosmin myocardial perfusion imaging for the noninvasive diagnosis of transplant coronary artery stenosis. J Heart Lung Transplant 2000; 19: 360.

27. Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. J Heart Lung Transplant 2010; 29: 717.

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