Transpl Int (2002) 15: 317–325
DOI 10.1007/s00147-002-0418-9

ORIGINAL ARTICLE

Bruno Schnetzler
Philippe Leger
Andreas Völp
Richard Dorent
Alain Pavie
Iradj Gandjbakhch

A prospective randomized controlled study on the efficacy and tolerance of two antilymphocytic globulins in the prevention of rejection in first-heart transplant recipients

Received: 21 August 2000
Revised: 24 January 2002
Accepted: 21 March 2002
Published online: 15 May 2002

B. Schnetzler (✉)
Cardiology Division,
Hôpitaux Universitaires de Genève,
24 rue Micheli du Crest,
1211 Geneva 4, Switzerland
E-mail: bruno.schnetzler@hcuge.ch
Tel.: +41-22-3723311
Fax: +41-22-3727229

B. Schnetzler · R. Dorent · A. Pavie
I. Gandjbakhch
Department of Cardiac Surgery,
La Pitié Salpétrière Hospital,
Paris, France

P. Leger
Department of Anesthesia and
Intensive Care,
La Pitié Salpétrière Hospital,
Paris, France

A. Völp
Fuchstanzstrasse 107,
60489 Frankfurt, Germany

Abstract The usefulness of induction phase treatment in heart transplantation is a long-standing debate in the literature. Several centers report good short-term survival without such treatment, but no randomized trial addresses this question. If induction treatment is to be used, most centers prefer rabbit polyclonal antisera to OKT3. However, again, no randomized trial has compared the relative efficacy and tolerance of rabbit antisera. Fifty first-heart transplant recipients with standard triple immunosuppression were randomized to receive ATG Fresenius ($n=24$) or Thymoglobulin Mérieux ($n=26$) as an induction treatment and were followed for 1 year. The two groups were well matched for gender, age, pre-transplant diagnosis and ischemia time. Actuarial survival at 1 year was 87.5% in the Fresenius group and 84.6% in the Mérieux group (Fisher's exact test; $P=1$). The average number of rejection episodes per patient was comparable in both treatment groups (Fresenius: mean = 2.63, SD = 1.44; Mérieux: mean = 2.46, SD = 2.04). Mean time to first rejection was 48.9 ± 37.2 days in the Fresenius group versus 59.6 ± 54 days in the Mérieux group (Mann-Witney U-test: $z=0.77$; $P=$ NS). The total number of rejections across all patients was also comparable (Fresenius: 63; Mérieux: 64) as well as the severity of rejection (seven moderate rejections out of a total of 63 in the Fresenius group and eight out of 64 in the Mérieux group). Eighteen Fresenius (75%) and 15 Mérieux (58%) patients suffered from at least one infection ($P=$ NS). The tolerance to treatment was excellent in both groups. Total lymphocyte count and all subsets of tested lymphocytes decreased rapidly after the introduction of either antiserum but was more pronounced and persisted for longer in the Mérieux group. ATG Fresenius or Thymoglobulin Mérieux as induction treatments in first-heart transplant recipients treated with standard immunosuppression have the same relative efficacy with regard to survival, acute rejection or infection rate, and are well tolerated.

Keywords Cardiac transplantation · Antilymphocyte globulins · Acute rejection

Abbreviations. *ATG* Antithymocyte globulins · *NS* Not significant · *CMV* Cytomegalovirus · *ECC* Extracorporeal circulation *TLC* Total lymphocyte count · *SGOT* Serum glutamic oxaloacetic acid transferase · *SGPT* Serum glutamic pyruvic acid transferase · *ISHLT* The International Society for Heart and Lung Transplantation

Introduction

Polyclonal antilymphocyte or ATGs were introduced in the late 1960s in the induction phase of immunosuppression in heart transplantation [5]. More recently, in the early 1980s, the murine monoclonal antibody OKT3 was also used as an induction treatment in heart transplantation. A few trials [6, 10, 12, 13, 14, 15, 17, 18], some of which were randomized [6, 12, 17, 18], comparing the relative efficacy and tolerance of the two treatments have been performed. These trials failed to show a difference in survival between patients undergoing the two treatments. However, Macdonald et al. showed an increased rate of infection in the OKT3-treated group, with an increased number of side effects [17], whereas Kormos et al. [12] showed a much more elevated rate of early rejection (less than 30 days) within the OKT3 group. Since then, the issue of the long-term safety of OKT3 has been addressed because of an increased rate of lymphoproliferative diseases [25]. The use of OKT3 in the induction phase of heart transplantation has declined since then, even though it is still used in some centers as a treatment in steroid-resistant acute rejection [7, 27].

Therefore, even if the adequacy of an induction treatment is still debated in the literature [20], the choice of antithymocyte or antilymphocyte globulins as opposed to OKT3 seems to be the best if any induction treatment has to be chosen. There is, however, a large choice of available polyclonal antilymphocytic preparations in clinical practice: horse versus rabbit antisera, antilymphocyte versus antithymocyte antisera, but no randomized, comparative study is available in the literature concerning this problem [9].

Therefore, we set up a prospective, randomized, open, unicenter, controlled study comparing the efficacy and safety of two largely used rabbit polyclonal antilymphocytic preparations: ATG Fresenius (Fresenius AG, Bad Homburg, Germany) and Thymoglobulin Mérieux (Pasteur Mérieux, Lyon Cedex, France). The main objectives of our study were to evaluate the efficacy of these two treatments with regard to patient survival and incidence and duration of rejection over a period of 1 year after transplantation. Moreover, we compared the tolerance of both drugs, focusing on the incidence of infection, pathological laboratory data and adverse events.

Patients and methods

Fifty consecutive patients were included in the study. Inclusion criteria were: first-heart transplantation, age of recipients between 16 and 60 years and written informed consent. Exclusion criteria were: second graft transplantation, serious concomitant diseases or severe thrombocytopenia, bacterial, viral or fungal infections upon inclusion, pregnancy or lactation, or previous treatment with rabbit polyclonal antilymphocytic preparations.

The study was conducted as a prospective, open, comparative, randomized, clinical phase-III trial. It was approved by the local ethical committee, and all enrolled patients signed an informed consent.

Twenty-four patients received induction treatment with ATG Fresenius and 26 with Thymoglobulin Mérieux. In the course of the 1-year follow-up, three patients from each treatment group dropped out prematurely.

Our immunosuppressive regimen was otherwise as follows [22]: methylprednisolone 240 mg intravenously and azathioprine 2 mg/kg intravenously pre-operatively and methylprednisolone 240 mg intra-operatively; cyclosporin 1–3 mg/kg intravenously, beginning between days 1 and 3 depending on renal or liver function, followed by 8–10 mg/kg/day taken orally and adjusted to maintain a trough level of 300 ng/ml by the whole blood monoclonal antibody assay; azathioprine 2 mg/kg/day taken orally postoperatively and adjusted to white blood cell count, and prednisone 1 mg/kg/day taken orally, begun at day 6 and tapered to 0.3 mg/kg/day at day 21.

The induction treatment was started on the first day after transplantation and was continued until day 5 after transplantation. Thymoglobulin Mérieux or ATG Fresenius was applied intravenously via a central catheter. The initial dosage was 3.0 mg/kg/day in the Fresenius group and 2.5 mg/kg/day in the Mérieux group. If the TLC exceeded 300/mm^3, the dosage was increased by 1 mg/kg/day.

All patients received, on a systematic basis, acetylsalicylic acid and dipyridamole begun on day 1 after transplantation, and sulfamethoxazole 120 mg/day begun 1 month after transplantation.

In the 1st week after transplantation, laboratory data were assessed daily. From the 2nd week until the 8th week these assessments were performed weekly, and then monthly up to the 12th month. The incidences of rejection, infection, change in vital signs, adverse event, and graft and patient loss were monitored for 1 year after transplantation. All CMV-positive recipients and all CMV-negative recipients who received a heart from a CMV-positive donor were submitted to CMV prophylaxis with ganciclovir for 2 weeks.

During the 1st month after transplantation, endomyocardial biopsies were conducted every week. The interval was then increased to 2 weeks during months 2 through 6, and to 2 months in the following 6 months [8].

Statistical analysis

Differences in incidence of rejection were analyzed by Fisher's exact test; number of rejections per patient by the Mann-Whitney U-test; and duration of rejections by Student's t-test.

For the analysis of the time intervals between transplantation on the one hand, and the first rejection episode and patient death on the other, standard life tables were computed for each treatment group by Kaplan-Meier methodology. For comparison of the survival functions obtained for ATG Fresenius and Thymoglobulin Mérieux, Gehan's generalized Wilcoxon test was employed.

Differences in survival curve were analyzed by the Wilcoxon (Gehan) test. A type-I error of 5% (two-tailed) was assumed.

One Fresenius patient and three Mérieux patients died shortly after transplantation without ever having had a rejection episode. These patients were treated as uncensored cases and were entered with their date of death as terminal events.

One patient randomized to the ATG Fresenius group received Thymoglobulin Mérieux by mistake. For data analysis purposes, he was assigned to the Mérieux group (as treated).

Results

Donor history, organ conservation and surgical considerations

The characteristics of the donors are listed in Table 1. The mean donor age, gender ratio, ischemia time and ECC time were comparable in both treatment groups.

All grafts were harvested by the same method and conserved with cold St. Thomas II solution. Cold blood cardioplegia was then used for the graft procedure with warm reperfusion at declamping (except for five patients). All transplantations were performed according to the classical technique of Lower and Shumway [16].

The average cold ischemia time was 125 min (SD ±44) and the average ECC time 96 min (SD ±25). In 62% of grafts the cold ischemia time was less than 2 h and in 38% between 2 and 4 h.

Recipient history and immune status

The characteristics of the patients are described in Table 2. There was no statistical difference between the two groups with regard to gender ratio, age, height, weight, smoking history, previous cardiac surgery or etiology of heart disease.

Approximately 90% of the patients in both treatment groups had HLA antigen mismatches of type A, B, and/or DR but there were no statistical differences between groups (data not shown). Cytotoxic antibodies were not found in any of the patients. Panel T- or B-lymphocyte reactivity was always below 50%. No cytotoxic antibodies or positive current B crossmatches were detected.

Table 1. Donor and surgical characteristics

Characteristic	ATG Fresenius	ATG Mérieux	*P*
Donor age (years)	38 ± 13[a]	36 ± 14[a]	NS
Donor gender (male/female)	20/4	20/6	NS
Ischemia time (min)	119 ± 38[a]	131 ± 49[a]	NS
ECC time (min)	93 ± 15[a]	99 ± 32[a]	NS

[a]Mean and SD

Table 2. Recipient characteristics and causes of heart failure

Characteristic	ATG Fresenius ($n=24$)	ATG Mérieux ($n=26$)	*P*
Gender (male/female)	20/4	20/6	NS
Age (years)	48 ± 10[a]	45 ± 11[a]	NS
Height (cm)	171 ± 6[a]	169 ± 9[a]	NS
Weight (kg)	68 ± 1[a]	67 ± 8[a]	NS
Smoking history (%)	58.7	42.3	NS
Previous cardiac surgery (%)	4.2	7.7	NS
Ischemic heart disease (%)	33.3	23.1	NS
Cardiomyopathy (%)	66.7	65.4	NS
Valvular disease (%)	0	3.8	NS
Other (%)	0	7.7	NS

[a]Mean and SD

Dosage of ATG

As shown in Fig. 1, the ATG dosage in the Fresenius group was 3 mg/kg at day 1 and was then slightly increased over time, reflecting a number of patients with a TLC in excess of 300/mm^3. In the Mérieux group (dosage 2.5 mg/kg), there was no need for further dosage adjustment.

CMV status and blood group

Nine Fresenius and 13 Mérieux donors were CMV positive. The numbers of CMV-positive recipients were 15 and 17, respectively. Five patients in each group showed the high-risk combination of donor positive/recipient negative.

All patients had identical blood groups, while rhesus was compatible in all patients except one from the Fresenius group and three from the Mérieux group.

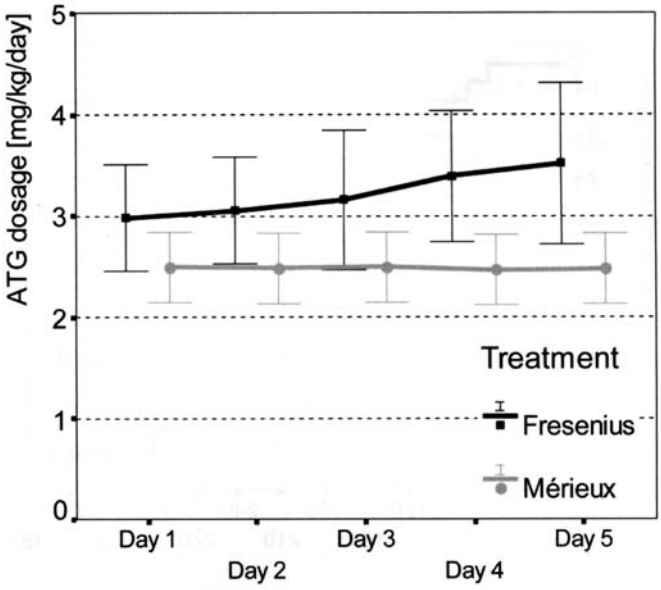

Fig. 1. ATG dosage during induction treatment: means and SDs

Patient survival

Actuarial survival is depicted in Fig. 2. The 1-year patient survival rates were 87.5% (21 out of 24) for the Fresenius group and 84.6% (22 out of 26) for the Mérieux group (Fisher's exact test; $P = 1.0$).

During the 1-year follow-up, seven patients died: three in the Fresenius group and four in the Mérieux group. Two patients died in the Fresenius group as a consequence of a 1st and 2nd rejection, 8 and 10 weeks, respectively, after the transplantation. One more patient in the Fresenius group died on day 6 from low cardiac output related to primary graft dysfunction. In the Mérieux group, one patient died during a first episode of acute rejection 9 months after transplantation. Three others patients died from causes unrelated to acute rejection: one from pneumonia-related hemoptysia 3 days after transplantation, one from circulatory collapse and pneumonia-related multiple organ failure 9 days after transplantation, and one from ventricular fibrillation attributed to primary graft dysfunction in a state of coma 19 days after transplantation.

Rejection episodes

According to the protocol, the diagnosis of rejection was retained by the investigator through a combination of clinical signs, heart biopsy and echocardiography. In the case of clinical evidence for rejection, a heart biopsy was to be performed immediately. In fact, all but two (one in each group) diagnoses of rejection were confirmed by heart biopsy. Rejection episodes were classified as mild, moderate or severe according to the Billingham classification [2]. Rejection occurred in 22 out of 24 patients in the Fresenius group and in 22 out of 26 in the Mérieux group. However, one of the two Fresenius patients and three of the four Mérieux patients who were free of rejection died shortly after transplantation. Some of the characteristics of acute rejection are shown in Table 3.

The number of rejections per patient is shown in Fig. 3. The average number of rejections per patient was comparable in both treatment groups (Fresenius: mean = 2.63, SD = 1.44; Mérieux: mean = 2.46, SD = 2.04). Mean time to first rejection was 48.9 ± 37.2 days in the Fresenius group versus 59.6 ± 54 days in the Mérieux group (Fig. 4). However, there were no indications for systematic inter-treatment differences (Mann-Witney U-test: $z = 0.77$; $P = 0.44$). The total number of rejections across all patients was also comparable (Fresenius: 63; Mérieux: 64) as well as the

Table 3. Characteristics of acute rejection (*AR*) in both groups of patients. *CHF* Congestive heart failure

Characteristic	Fresenius	Mérieux	*P*
Mean no. of ARs/patient	2.9 ± 1.2	2.9 ± 1.9	NS
Total no. of AR episodes	63	64	NS
Histological grading of AR			
Mild	56	56	NS
Moderate	7	8	NS
Clinical signs			
No data (%)	3.2	3.1	NS
No clinical signs (%)	81	78.1	NS
Left CHF (%)	3.2	3.1	NS
Right CHF (%)	9.5	12.5	NS
ECG changes (%)	3.2	3.1	NS
Median time to first rejection (days)	41.5	48	NS
Mean duration of AR (days)[a]	13 ± 18	11 ± 5	NS

[a]Time from the first biopsy showing rejection to the first normal biopsy

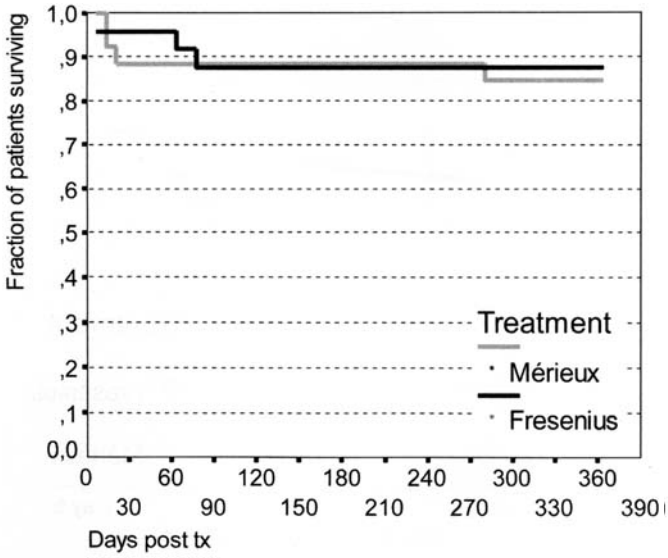

Fig. 2. Kaplan-Meier survival curves

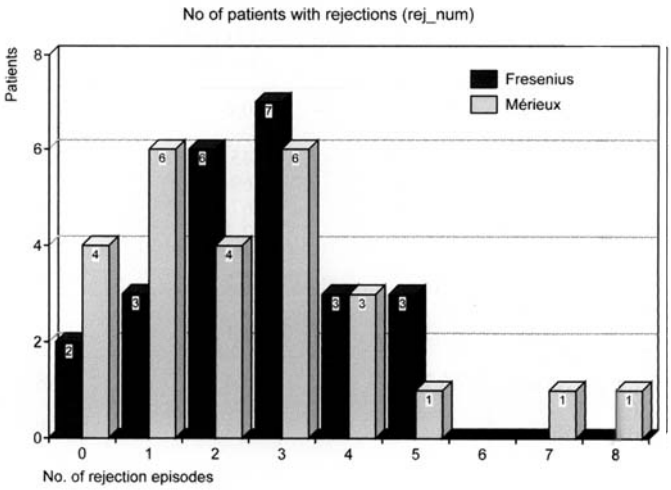

Fig. 3. Rejections per patient within the 1st year

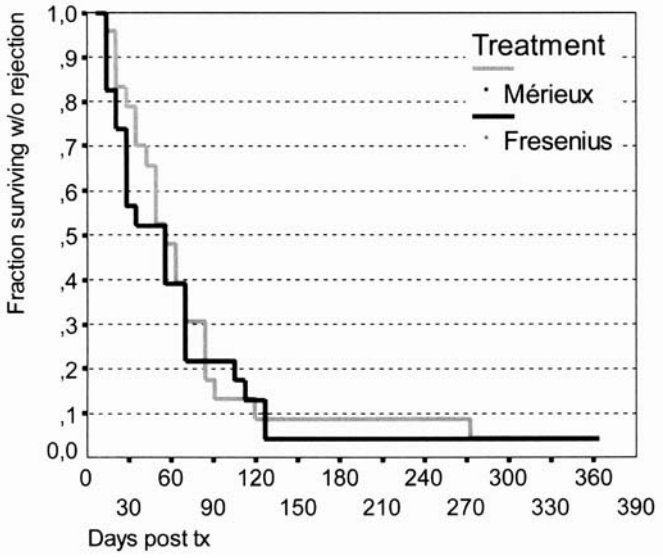

Fig. 4. Rejection-free survival (time to first rejection). Both curves are identical from day 266

histological grading of rejection (seven moderate episodes out of a total of 63 in the Fresenius group and eight out of 64 in the Mérieux group). Signs of congestive heart failure were present in the same proportion in both groups (12.7% and 15.6% in the Fresenius and Mérieux groups, respectively). Duration of rejections was also similar (data not shown).

Incidence of infections

During follow-up, 18 Fresenius patients (75%) and 15 Mérieux patients (58%) suffered from at least one infection (P = NS). The number of infections per patient was between 1 and 6 in the Fresenius group and between 1 and 3 in the Mérieux group. The most frequent single cause of infection across both treatment groups was CMV (Fresenius: eight; Mérieux: five) (Table 4). Five out of eight Fresenius patients with CMV infections were donor negative/recipient positive, while in the Mérieux group, four out of five were donor positive/recipient positive. Among the 'high-risk' patients who were donor positive/recipient negative, two treated with ATG Fresenius and one treated with ATG Mérieux actually developed CMV infection during follow-up.

The other types of frequent infections were bacterial sepsis (Fresenius: six; Mérieux: four) and herpes zoster (three and seven respectively).

Tolerance to treatment

The tolerance to treatment was excellent in both groups. In particular, there were no reported cases of acute serum sickness, skin rashes, or muscular or joint pain. Fever was noted in 6% of cases without any significant difference between the two groups.

Table 4. Infections in the 1st year after transplantation

Infection	Fresenius %	Mérieux %	P
Total bacterial[a]	58.3	38.5	NS
Wound	12.5	7.7	
Urinary tract	12.5	3.8	
Pneumonia	25	11.5	
Sepsis	25	15.4	
Other	12.5	7.7	
Total viral[a]	45.8	46.2	NS
CMV	33.3	19.2	
Herpes zoster	12.5	26.9	
Other	4.2	3.8	
Fungal	4.2	0	NS
Candida	0	0	
Aspergillus	0	0	
Other	4.2	0	
Parasitic	0	0	NS
Total patients			
With infections	75	57.7	NS
Without infection	25	42.3	NS
Mean (SD) duration of infections	21 ± 13	20 ± 14	NS

[a]Some patients suffered from more than one infection

Laboratory data

As could be expected, several laboratory parameters were abnormal after transplantation. There were, however, no significant differences between the Fresenius and Mérieux groups concerning the following parameters: natremia, kaliema, chloride, serum bicarbonate, creatinine, SGOT, SGPT, fibrinogen, prothrombin time and partial thromboplastin time (data not shown).

TLC decreased rapidly after the introduction of either antiserum but the decline was more pronounced in the Mérieux group (Fig. 5). The bottom value of TLC was 409/mm^3 at day 3 in the Fresenius group and 158/mm^3 at day 4 in the Mérieux group. After that, there was a slow, regular increase in TLC. Fifty percent of the patients had a TLC above 300/mm^3 at day 6 in the Fresenius group and at week 3 in the Mérieux group. The mean TLC was again above 1,000/mm^3 at week 8 and month 8 in both groups, respectively.

The number of CD3, CD4, CD8 and CD11 lymphocytes was also consistently lower in the Mérieux group throughout the entire period of induction, with a pattern similar to that of TLC (data not shown).

Figure 6 shows the time course of leukocyte counts. There was an expected first peak soon after surgery (day 2) and then a decrease secondary to the induction treatment and a rebound peak at week 2. The mean

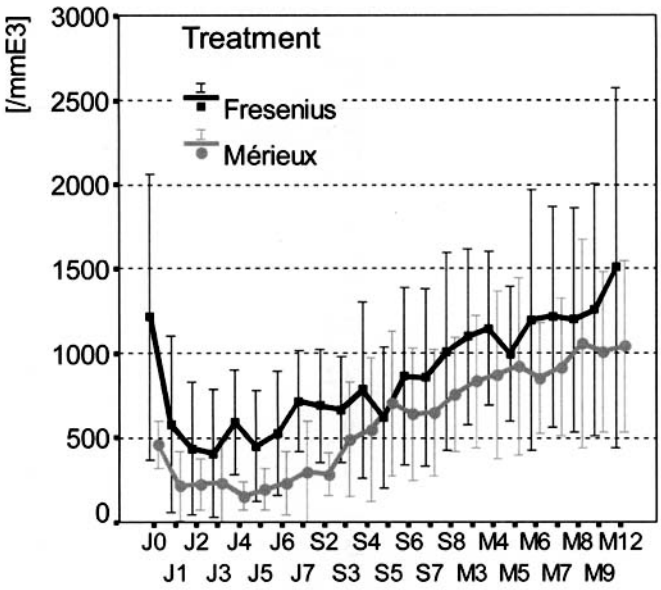

Fig. 5. Total lymphocyte count (means and SDs)

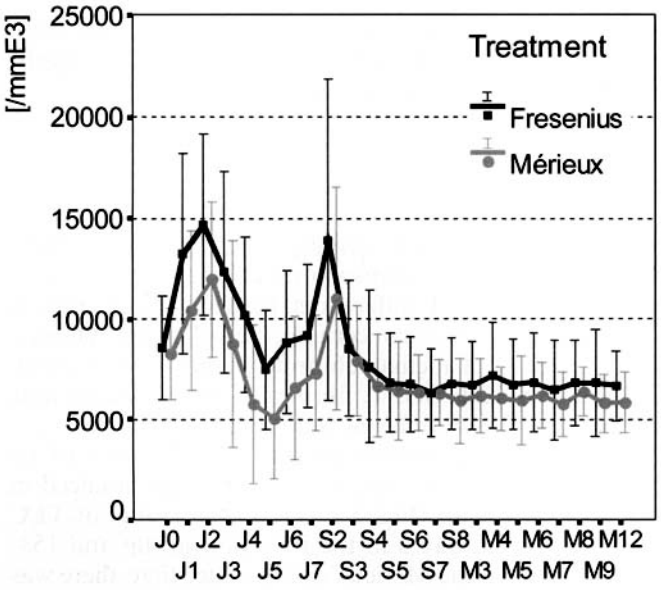

Fig. 6. Leukocyte count time course (means and SDs)

number of leukocytes was consistently more elevated in the Fresenius group, especially during the first 2 weeks.

The number of platelets decreased slightly after surgery with a bottom value at day 3 and then a sharp increase with a pronounced rebound that peaked at week 2. Platelets were consistently more elevated in the Fresenius group (Fig. 7). There was no hemorrhagic problem reported in either group.

Numbers of erythrocytes decreased slightly but rapidly (day 1) after transplantation in both groups but

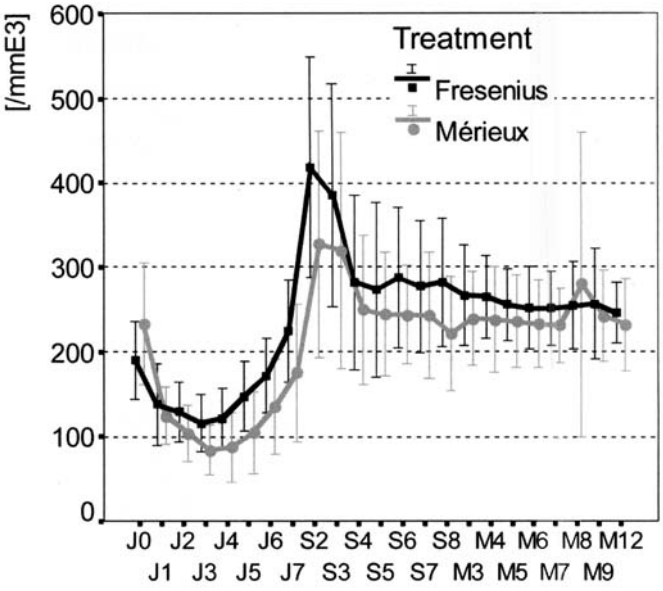

Fig. 7. Platelet count time course (means and SDs)

were more pronounced in the Fresenius group (Fig. 8). The bottom value was reached at week 2 with a subsequent gradual increase to plateau at a value slightly inferior to the baseline value.

Discussion

The usefulness of induction phase treatment in heart transplantation is a long-standing debate in the litera-

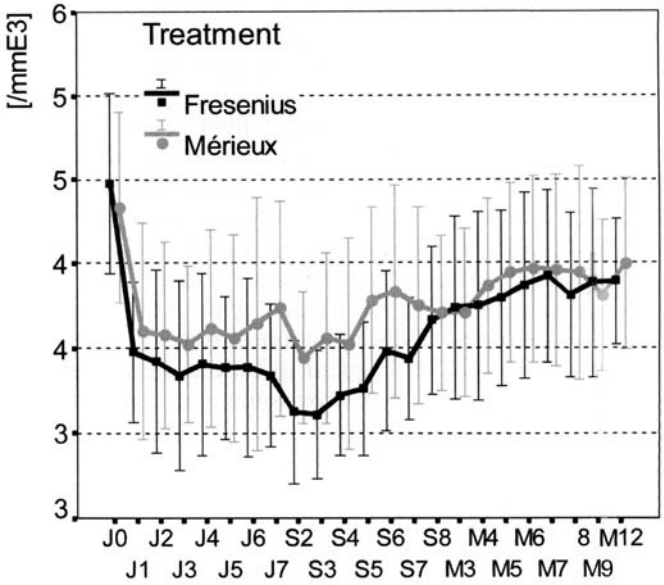

Fig. 8. Erythrocyte count time course (means and SDs)

ture. Several centers report good short-term survival results without the use of such treatment. However, no randomized trial has addressed this problem and many transplant centers still use induction phase treatment. The results of a recently published study [9] comparing the use of Sandimmun versus Neoral in first-heart transplant recipients are particularly interesting in this regard. Around 40% of the patients received (according to each center's usual practice) peri-operative antilymphocyte antibodies, with the same proportion in the Sandimmun and Neoral groups. In a post-hoc analysis, the authors showed that antilymphocyte antibody induction therapy decreased the incidence of ISHLT ≥3A cardiac allograft rejection in a statistically significant manner (6 months results). In the European multicenter tacrolimus heart pilot study [20] comparing the use of FK506 and cyclosporin in heart transplantation, a subset of patients (according again to each center's usual practice) received induction with polyclonal antilymphocytic preparations. The patients who received polyclonal antilymphocytic preparations, compared to those who did not, had a higher 1-year acute rejection-free rate (49.2% and 26.7%, respectively; $P = 0.08$).

There are, on the contrary, several trials which have addressed the question of the relative efficacy of polyclonal antilymphocytic preparations against the monoclonal antibody OKT3 [6, 10, 12, 13, 14, 15, 17, 18]. These trials have failed to show an improved efficacy of this monoclonal antibody and have even raised the question of increased short-term (more infection) and long-term (more lymphoproliferative disorder) deleterious side-effects. Other monoclonal antibodies (like anti-IL2 receptor antibodies) have been used with success in renal [24, 26], and more recently heart, transplantation [1]. Nevertheless, the question of the relative efficacy of the polyclonal antilymphocytic preparations is still open. Rabbit polyclonal antilymphocytic preparations are such available treatments and are largely used in common clinical practice. When compared with horse antisera, they appear to have better batch-to-batch reliability concerning their immunosuppressive properties and are responsible for less serum sickness [11]. There may exist, however, some differences in the antigens present on the cell surfaces of the immunogenic cells used in the different rabbit antilymphocytic preparations (human thymocytes or T lymphoblasts) and therefore in the epitopes of the polyclonal antibodies induced [19]. Indeed, there has been one study reporting different levels and specificities in the antibodies produced by antilymphocyte and ATGs, both from horse and rabbit origin [3]. In the case of rabbit antisera (immunized with thymocytes or T lymphoblasts), antibodies against CD3, CD5, CD11a, CD18, CD45 and B2 microglobulins were found with marked differences in the levels of antibodies in the different preparations, even if it was clearly stated by the authors that the different levels and specificities of the antibodies were of unknown clinical relevance.

Moreover, there has been a study reporting much higher levels of in-vivo production of IL6 or TNF-alpha using prophylactic Thymoglobulin Mérieux compared with Stanford ATG in heart transplantation [10]. In the same study the levels of IL10 and IL4 were also more elevated in the Mérieux group, but to a lesser extent. No cytokine release syndrome was present in either group. The authors then compared the ability of four polyclonal antilymphocytic preparations (including several different batches of Mérieux and Upjohn ATG) to elicit in-vitro IL6 production. There were major differences in this regard between the manufacturers. The only batch of ATG Fresenius tested gave the higher level of IL6, whereas the nine Thymoglobulin Mérieux batches gave an intermediate level (with good batch-to-batch reliability) and the unique Stanford and three Upjohn (also with good reliability between batches) batches gave low levels of IL6. Again, the clinical relevance of these different levels of interleukin production, with regard to their immunosuppressive properties, is unknown [12, 21].

It was, therefore, of clinical interest to compare the relative efficacy and tolerance of ATG Fresenius and Thymoglobulin Mérieux, which are largely used all over Europe and in the US. Thymoglobulin Mérieux is derived from human thymocytes (typically obtained during cardiothoracic pediatric procedures), whereas ATG Fresenius is produced from the Jurkat cell line derived from human activated lymphocytes.

The dosage of ATG Fresenius at 3 mg/kg that we used was slightly inferior to that recommended by the company, between 4 and 5 mg/kg. We chose this dosage, however, because of concern for over-immunosuppression. We had to increase this dosage to 3.5 mg/kg in an attempt to decrease (unsuccessfully) the number of lymphocytes under $300/mm^3$.

However, the results showed that 1-year survival in both treatment groups was over 90% and was not different between the two groups.

The acute rejection process which occurred in almost all patients was comparable in both groups: the same average number of rejection episodes per patient, and the same total number, duration, and severity (as assessed by histological grading and number of patients with signs of congestive heart failure) of rejection episodes. Time to first rejection was shorter in the Fresenius group, but this difference was not statistically significant.

The incidence of infection was also not statistically different between the two groups (75% and 58% in the Fresenius and Mérieux groups, respectively). The microorganisms involved, time-course (according to the date of transplantation), and severity of infections were the same in both groups.

It is of importance to note that tolerance was excellent in both groups. The slight differences in the erythrocyte count (more elevated in the Mérieux group) or the platelet count (more elevated in the Fresenius group) were of no clinical relevance in our patients, but still could be of clinical interest in specific cases (i.e., patients with important thrombocytopenia, where ATG Fresenius could be more appropriate).

According to the clinical results, which seem to show equivalent short-term efficacy and tolerance to Fresenius and Mérieux antilymphocytic preparations, it is difficult to interpret the clinical relevance of the more important drop in the TLC (and of all the subsets of T lymphocytes tested) in the Mérieux group. It is of importance to note in this regard, that polyclonal antilymphocytic preparations have an immunosuppressive effect that is partially related to their immunoregulatory action on lymphocytes [3, 4, 23]. The heterogeneity of the different antilymphocytic preparations may have an influence on their respective lymphopenic powers and on their immunoregulatory properties as well. Would a more powered study have shown a difference in the incidence of acute rejection, infection or even death in one group (type-II statistical error)? Or, on the contrary, would a long-term follow-up show an increased morbidity (particularly in the incidence of lymphoproliferative disease) in the over-immunosuppressed group? It is not possible at the moment to answer these questions.

Clinical practitioners who believe that the total number of lymphocytes should be less than 300/mm^3 at the time of induction should certainly increase the dosage of ATG Fresenius to more than 3.5 mg/kg, according to our results.

This trial did not demonstrate equivalence between the two treatments (because it was intended as a superiority trial), but it also did not indicate in any way that there were any differences in efficacy of Thymoglobulin Mérieux against ATG Fresenius.

In our institution, ATG Fresenius and Thymoglobulin Mérieux are used indifferently for induction treatment in heart transplantation.

References

1. Beniaminovitz A, Itescu S, Lietz K, Donovan M, Burke EM, Groff BD, Edwards N, Mancini DM (2000) Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med 342: 613–619
2. Billingham ME (1982) Diagnosis of cardiac rejection by endomyocardial biopsy. J Heart Transplant 1:25–30
3. Bonnefoy-Berard N, Revillard JP (1996) Mechanisms of immunosuppression induced by antithymocyte globulins and OKT3. J Heart Lung Transplant 15:435–442
4. Bonnefoy-Berard N, Vincent C, Revillard JP (1991) Antibodies against functional leucocyte surface molecules in polyclonal antilymphocyte and antithymocyte globulins. Transplantation 51:669–673
5. Carey JA, Frist WH (1990) Use of polyclonal antilymphocyte preparations for prophylaxis in heart transplantation. J Heart Transplant 9:297–300
6. Costanzo-Nordin MR, O'Sullivan EJ, Johnson MR, Winters GL, Pifarre R, Radvany R, Zucker MJ, Scanlon PJ, Robinson JA (1990) Prospective randomized trial of OKT3 versus horse antithymocyte globulin-based immunosuppressive prophylaxis in heart transplantation. J Heart Transplant 9: 306–315
7. Deeb GM, Bolling SF, Steimle CN, Dawe JE, McKay AL, Richardson AM (1991) A randomized prospective comparison of MALG with OKT3 for rescue therapy of acute myocardial rejection. Transplantation 51: 180–183
8. Desruennes M, Corcos T, Cabrol A, Gandjbakhch I, Pavie A, Leger P, Eugen M, Bors V, Cabrol C (1988) Doppler echocardiography for the diagnosis of acute cardiac allograft rejection. J Am Coll Cardiol 12: 63–70
9. Eisen HJ, Hobbs RE, Davis SF, Laufer G, Mancini DM, Renlund DG, Valantine H, Venture H, Vachiery JL, Bourge RC, Canver CC, Carrier M, Costanzo MR, Copeland J, Dureau G, Frazier OH, Dorent R, Hauptman PJ, Kells C, Master R, Michaud JL, Paradis I, Smith A, Vanhaecke J, Mueller EA et al. (1999) Safety, tolerability and efficacy of cyclosporine microemulsion in heart transplant recipients: a randomized, multicenter, double-blind comparison with the oil-based formulation of cyclosporine – results at six months after transplantation. Transplantation 68:663–671
10. Grant SC, Lamb WR, Yonan N, Hutchinson IV, Brenchley PEC (1995) Antithymocyte globulin preparations after heart transplantation. Cytokine responses in vivo and in vitro. Transplantation 60:684–689
11. Ippoliti G, Rovati B, Graffigna A (1989) Prophylactic use of rabbit ATG vs horse ALG in heart-transplanted patients under Sandimmun (CyA) therapy: clinical and immunological effects. Clin Transplant 3:1–5
12. Kormos RL, Armitage JM, Dummer JS, Miyamoto Y, Griffith BP, Hardesty RL (1990) Optimal perioperative immunosuppression in cardiac transplantation using rabbit antithymocyte globulin. Transplantation 49:306–311
13. Ladowski JS, Dillon T, Schatzlein MH, Peterson AC, Deschner WP, Beatty L, Sullivan M, Scheeringa RH, Clark WR (1993) Prophylaxis of heart transplant rejection with either antithymocyte globulin, Minnesota antilymphocyte globulin, or an OKT3-based protocol. J Cardiovasc Surg 34:135–140
14. Laske A, Gallino A, Schneider J, Bauer EP, Carret T, Pasic M, von Segesser LK, Turina MI (1992) Prophylactic cytolytic therapy in heart transplantation: monoclonal versus polyclonal antibody therapy. J Heart Lung Transplant 11:557–563
15. Laufer G, Laczkowics A, Wollenek G, Schreiner W, Sochor H, Holzinger C, Buchelt M, Fasol R, Wolner E (1989) Impact of low-dose steroids and prophylactic monoclonal versus polyclonal antibodies on acute rejection in cyclosporine- and azathioprine-immunosuppressed cardiac allografts. J Heart Transplant 8:253–261

16. Lower RR, Shumway NE (1960) Studies on orthotopic transplantation of the canine heart. Surg Forum 11:18–20
17. Macdonald PS, Mundy J, Keogh AM, Chang VP, Spratt PM (1993) A prospective randomized study of prophylactic OKT3 versus equine antithymocyte globulin after heart transplantation-increased morbidity with OKT3. Transplantation 55:110–116
18. Menkis AH, Powell AM, Novick RJ, McKenzie FN, Dostuk WJ, Pflugfelder PW, Brown JE, Rochon J, Chow LH, Stiller C (1992) A prospective randomized controlled trial of initial immunosuppression with ALG versus OKT3 in recipients of cardiac allografts. J Heart Lung Transplant 11:569–576
19. Raefsky EP, Gascon P, Gratwohl A, Speck B, Young NS (1986) Biological and immunological characterization of ATG and ALG. Blood 68:712–719
20. Reichart B, Meiser B, Vigano M, Rinaldi M, Yacoub M, Banner NR, Gandjbakhch I, Dorent R, Hetzer R, Hummel M (2001) European multicenter tacrolimus heart pilot study: three years follow-up. J Heart Lung Transplant 20:249–250
21. Renlund DG, O'Connell JB, Bristow MR (1989) Early rejection prophylaxis in heart transplantation: is cytolytic therapy necessary? J Heart Transplant 8:191–193
22. Schnetzler B, Pavie A, Dorent R, Camproux AC, Leger P, Delcourt A, Gandjbakhch I (1998) Heart retransplantation. A 23-year single-centre clinical experience. Ann Thorac Surg 65:978–983
23. Smith AG, O'Reilly RJ, Hansen JA, Martin PJ (1985) Specific antibody-blocking activities in antilymphocyte globulins as correlates of efficacy for the treatment of aplastic anemia. Blood 66:721–723
24. Soulillou JP, Cantarovich D, Le Mauff B, Giral M, Robillard N, Hourmant M, Hirn M, Jacques Y (1990) Randomized controlled trial of a monoclonal antibody against the interleukin-2 receptor (33B3.1) as compared with rabbit antithymocyte globulin for prophylaxis against rejection of renal allografts. N Engl J Med 322:1175–1182
25. Swinnen LF, Costanzo-Nordin M, Fisher SG, O'Sullivan EJ, Hohnson MR, Heroux AL, Dizikes GJ, Pifarre R, Fisher RI (1990) Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 323:1723–1728
26. Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran Neylan J, Wilkinson A, Ekberg H, Gaston R, Backman L, Burdick J (1998) Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. N Engl J Med 338:161–165
27. Wagner FM, Reichenspurner H, Uberfuhr P, Kur F, Kaulbach HG, Meiser BM, Ziegler U, Reichart B (1994) How successful is OKT3 rescue therapy for steroid-resistant acute rejection episodes after heart transplantation? J Heart Lung Transplant 13:438–443