How to use sirolimus in order to increase survival in heart transplant recipients?

Jak użyć sirolimusu, aby uzyskać poprawę przeżycia chorych po transplantacji serca?

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Abstract

Aim: Aim of the study was to was to assess the impact of sirolimus used as part of immunosuppressive therapy on survival of orthotopic heart transplantation (OHT) recipients. Material and methods: We performed a retrospective case-control study involving all 60 OHT recipients receiving sirolimus (study group), and 60 matched individuals treated without sirolimus (control group). In almost half of the study group sirolimus was used briefly, or introduced late after OHT. However, we identified 31 pts. in whom sirolimus was introduced before the 3rd year post-transplant, and continued permanently (28M/3F, 45 ±11y/o, ischaemic cardiomyopathy in 15 pts.). Sirolimus was combined with low-dose cyclosporine-A, replaced with mycophenolate mofetil 3 years post-transplant. The study subgroup was compared with its matches from the control group (28M/3F, 44 ±11y/o, ischaemic c-pathy in 17 pts.). We compared time free from all-cause death, cardiac death and non-cardiac death.

Results: Average follow-up was 2138 ±1192 days in the study group and 1949 ±1221 days in the control group (2169 ±650 vs. 1872 ±987 days, respectively in substudy). Fourteen (33%) deaths occurred in the study group and 25 (42%) in the control group (p = 0.032) – 5 (16%) deaths in the study subgroup vs. 14 (45%) deaths in the control subgroup (p = 0.028). Time free from all-cause death was significantly longer both in the whole study group and the subgroup (p = 0.044 and p = 0.019, respectively). The same trend was observed for the time free from non-cardiac death (p = 0.036 and p = 0.022, respectively).

Conclusion: A combination of sirolimus with low-dose cyclosporine-A prolongs survival in OHT recipients, decreasing probability of non-cardiac death.

Key words: heart transplantation, sirolimus, survival.

Streszczenie

Cel pracy: Celem badania była ocena, czy zastosowanie sirolimusu jako elementu terapii immunosupresyjnej może mieć wpływ na przeżycie biorców ortotopowego przeszczepu serca (OHT).

Materiał i metody: Przeprowadzono retrospektywne badanie kliniczno-kontrolne, do którego włączono 60 pacjentów po OHT otrzymujących sirolimus (grupa badana) i 60 dobranych indywidualnie chorych leczonych bez udziału sirolimusu (grupa kontrolna). U prawie połowy chorych z grupy badanej sirolimus był stosowany krótko lub włączono go późno po OHT. Jednak u 31 pacjentów (28 M/3 K, 45 ±11 lat, kardiomiopatia niedokrwienna przed OHT u 15 chorych) włączono go przed końcem 3. roku po OHT i stosowano w sposób permanentny. Sirolimus był stosowany w połączeniu z małą dawką cyklosporyny A, którą zastępowano mykofenolanem mofetylu po upływie 3 lat od OHT. Podgrupa ta została porównana z odpowiadającymi im uczestnikami grupy kontrolnej (28 M/3 K, 44 ±11 lat, kardiomiopatia niedokrwienna przed OHT u 17 chorych). Porównano czas wolny od zgonu z jakichkolwiek przyczyn oraz z przyczyn kardiologicznych i niekardiologicznych.

Wyniki: Średni czas obserwacji wyniósł 2138 ±1192 dni w grupie badanej i 1949 ±1221 dni w grupie kontrolnej (2169 ±650 i 1872 ±987 dni w odpowiednich podgrupach). Czternaście (33%) zgonów odnotowano w grupie badanej, a 25 (42%) w grupie kontrolnej (p = 0,032) – w podgrupach było to odpowiednio 5 (16%) i 14 (45%) zgonów (p = 0,028). Czas wolny od zgonu ze wszystkich przyczyn był istotnie dłuższy w grupie i podgrupie badanej (odpowiednio p = 0,044 i 0,019), podobnie jak w przypadku zgonu z przyczyn niekardiologicznych (p = 0,036 i 0,022).

Wniosek: Połączenie sirolimusu z małą dawką cyklosporyny A wydłuża okres przeżycia po OHT, zmniejszając prawdopodobieństwo zgonu z przyczyn niekardiologicznych.

Słowa kluczowe: transplantacja serca, sirolimus, przeżycie.

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Introduction

Introduction of sirolimus (SIR) to clinical immunosuppressive therapy of heart transplant recipients was undertaken in order to fight two main graft-related causes of death: acute rejection in the 1st year after orthotopic heart transplantation (OHT), and coronary artery vasculopathy typical for the late period after surgery. It was found that a combination of calcineurin inhibitor and SIR is a very potent protection against acute rejection, although SIR enhances toxicity of cyclosporine-A (CyA) and tacrolimus (TAC) used in their typical doses [1, 2], that SIR is able to slow the formation of intimal proliferation in transplanted heart coronary arteries [1], and that SIR introduced in patients with established transplanted heart coronary artery disease reduces the number of further cardiac events [3]. However, none of these studies were able to prove a survival benefit in OHT recipients receiving SIR. Together with disappointment caused by the high frequency of surgical wound healing complications [4, 5], this was a reason why SIR did not become a common element of immunosuppressive protocols worldwide, as reported by the registry of the International Society for Heart and Lung Transplantation (ISHLT) [5].

SIR was used in heart transplant patients of the Silesian Centre for Heart Disease for a number of indications from 2001. From the beginning, our intention was to utilize the antiproliferative activity of SIR in low-toxic combinations with limited doses of calcineurin inhibitors or even protocols avoiding the use of CyA or TAC directly after OHT. The aim of this study was to assess the impact of SIR used as part of immunosuppressive therapy on survival of OHT recipients.

Material and methods

We performed a retrospective case-control study involving all 60 OHT recipients receiving SIR (study group), and 60 matched individuals treated without SIR (control group). Due to a limited number of potential candidates for matched controls the following order of comparative factors was taken into consideration: sex (100% consistency), age of recipients (average difference 2.4 ±2.1 years), date of OHT (average difference 274 ±226 days), and indication for OHT (88% consistency). As a consequence the characteristics of the study and control group were as follows: 54 males and 6 females in each group, age of recipients 46.2 ±11 vs. 46.1 ±11 years, age of donors 30.5 ±10 vs. 31.2 ±11 years, ischaemic heart disease as an indication for OHT in 47 vs. 48% of patients, ischaemic time 193 ±73 vs. 184 ±42 minutes.

Indications to use SIR in patients from the study group were as follows: perioperative prophylaxis of renal failure in 26 patients (43%), refractory rejection in 22 patients (37%), prophylaxis of renal failure late after OHT in 6 patients (10%), neoplasm in 3 patients (5%), coronary vasculopathy in 2 patients (3%), and intolerance of mycophenolate mofetil in 1 patient (2%). Predominant primary immunosuppressive combinations in the study group were: CyA+ azathioprine (AZA)+ prednisone (P) – 22 patients, CyA+ mycophenolate mofetil (MMF)+ P – 15 patients, CyA+SIR+P – 8 patients, and SIR+MMF+P – 5 patients, while the control group was treated most often with: CyA+AZA+P – 34 patients, and CyA+MMF+P – 19 patients. TAC was used in 7 patients from the study group, and 5 patients from the control group. CyA was dosed according to the whole blood trough level, predefined for a particular drug combination and time after OHT: in patients receiving SIR it was 100-150 ng/mL in the 1st year post-OHT, and 50-100 ng/mL thereafter; in patients receiving MMF it was 250-300 ng/ml in the 1st year post-OHT, 150-250 ng/ml in the 2nd and 3rd year post-OHT, and 100-150 ng/ml thereafter; in the remaining patients it was 300-400 ng/ml in the 1st year post-OHT, 200-300 ng/ml in the 2nd and 3rd year post-OHT, and 100-200 ng/ml thereafter. SIR was dosed according to the whole blood trough level: 8-12 ng/ml in patients receiving calcineurin inhibitors, and 12-20 ng/ml in patients without CyA or TAC.

In almost half of pts. SIR was used for a short period early after transplant (mostly as prophylaxis of perioperative renal failure), or introduced late after the procedure (in patients with renal failure late after transplantation, with coronary vasculopathy, and neoplasms). However, we identified 31 pts. in whom SIR was introduced before the 3rd year post-transplant, and continued for at least 3 years, or until the end of observation (28M/3F, 45 ±11 y/o, ischemic cardiomyopathy in 15 pts.). The majority of them received a combination of SIR and low-dose CyA, which was replaced with MMF at the end of the 3rd year post-OHT (at the end of the observation 21 patients were without calcineurin inhibitor). They were compared with their matches from the control group (28M/3F, 44 ±11 y/o, ischaemic cardiomyopathy in 17 pts.).

Acute rejection was recognized based on results of endomyocardial biopsies that were obtained every week between the 1st and 4th week, every 2 weeks until the 8th week, every 3 months between the 3rd and 12th month, and in the 18th, 24th and 36th month post-OHT. Significance of the rejection was assessed using the International Society for Heart and Lung Transplantation (ISHLT) grading system, with grade ≥ 3A recognized as significant, according to the working formulation published in 1990 [7].

Renal function was assessed by serum creatinine concentration measured at the end of the 1st hospitalization, at the end of the 1st year post-OHT, and at the end of observation.

We compared number and cause of deaths, and time free from all-cause, cardiac, and non-cardiac death in patients from the study vs. control group and subgroup. Additionally, we compared the number of significant rejection episodes, and creatinine levels. Significance was assessed using chi-square test, log-rank test and Mann-Whitney U test when applicable.

Results

Average follow-up was 2138 ±1192 days in the study group and 1949 ±1221 days in the control group (2169 ±650

vs. 1872 ±987 days, respectively in subgroups). Fourteen (33%) deaths occurred in the study group and 25 (42%) in the control group (p = 0.032) – 5 (16%) deaths in the study subgroup vs. 14 (45%) deaths in the control subgroup (p = 0.028). Causes of death in the study vs. control group were as follows: primary graft failure (4), coronary vasculopathy (2), infections (2), acute rejection caused by non-compliance (1), sudden cardiac death (1), constrictive pericarditis (1), neoplasm (1), liver failure (1), missing data (1), vs. coronary vasculopathy (6), infections (5), acute rejection (3), neoplasm (3), liver failure (3), primary graft failure (2), sudden cardiac death (2), missing data (1). Causes of death

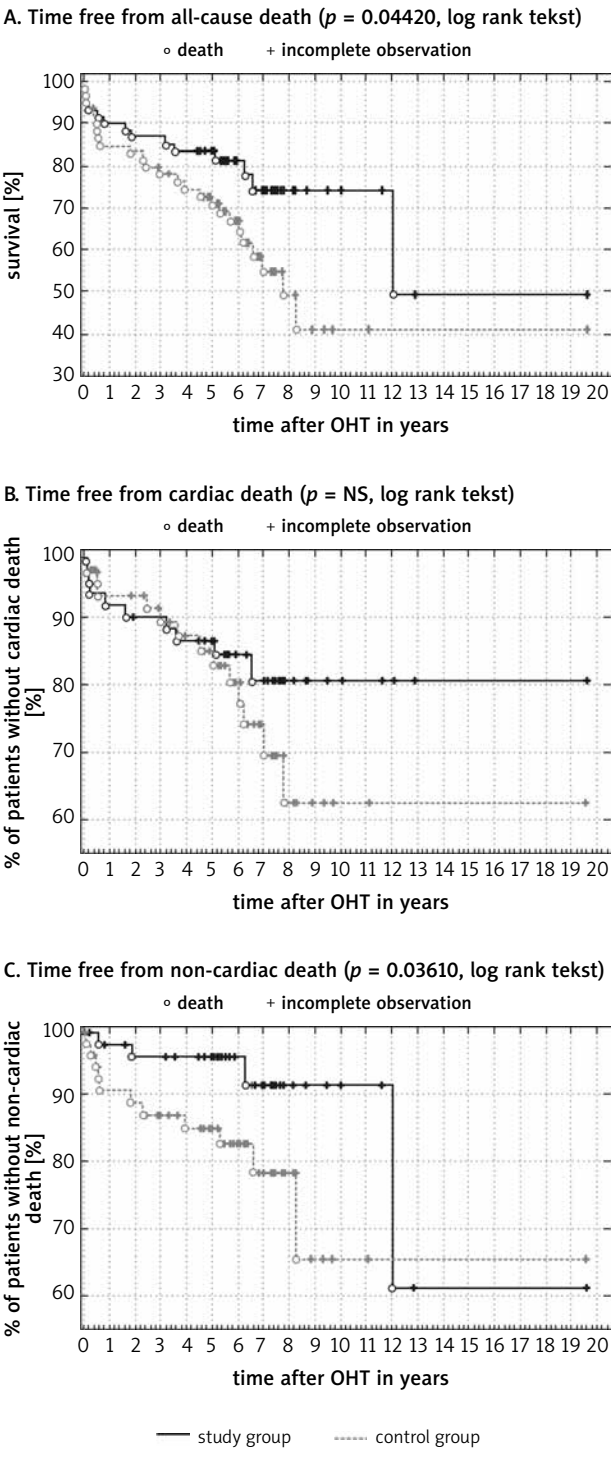

Fig. 1. Freedom from all-cause (panel A), cardiac (panel B), and non-cardiac death (panel C) in study vs. control group (n = 60 in each group)

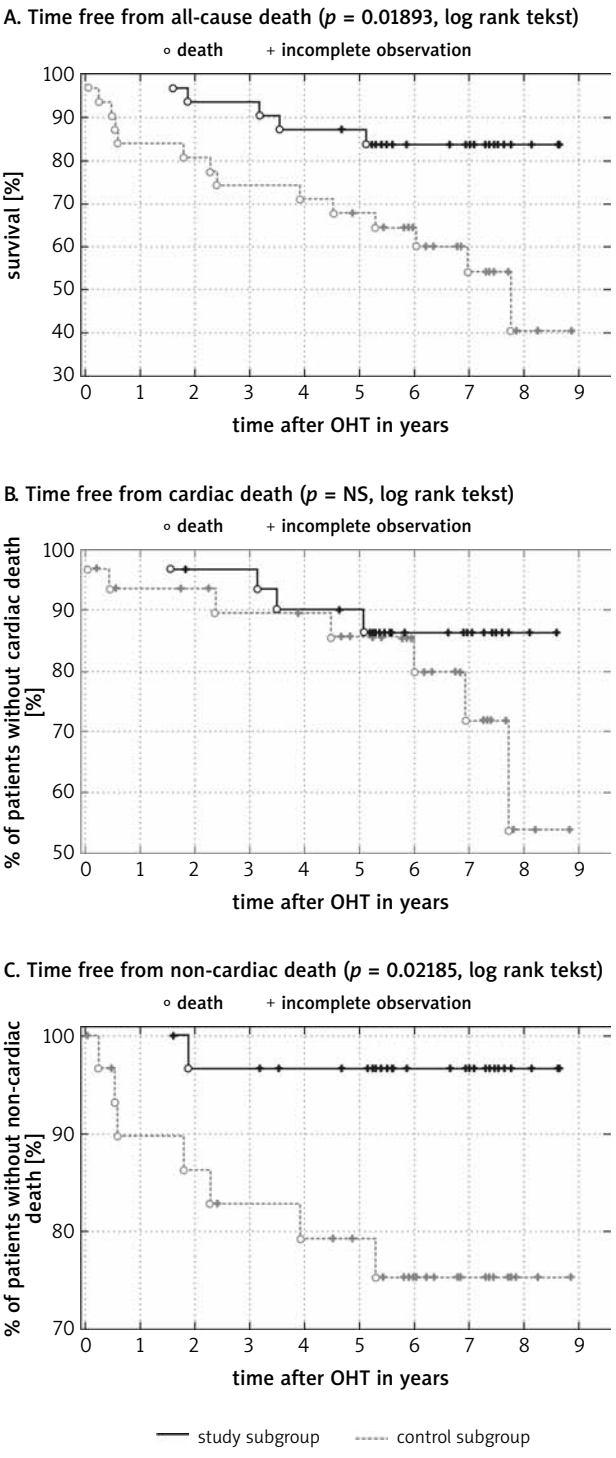

Fig. 2. Freedom from all-cause (panel A), cardiac (panel B), and non-cardiac death (panel C) in study vs. control subgroup (n = 31 in each group)

in the study vs. control subgroup were as follows: coronary vasculopathy (1), acute rejection caused by non-compliance (1), sudden cardiac death (1), neoplasm (1), missing data (1), vs. acute rejection (3), infections (3), neoplasm (2), liver failure (2), coronary vasculopathy (1), primary graft failure (1), sudden cardiac death (1), missing data (1).

Time free from all-cause, and non-cardiac death was significantly longer both in the whole study group and the subgroup when compared with matched controls (p = 0.044 and p = 0.019, respectively for all-cause death, and p = 0.036 and p = 0.022 for non-cardiac death, respectively). Difference in time free from cardiac death assessed between study and control groups and subgroups was insignificant (Fig. 1 and 2).

At least one episode of biopsy-proven significant rejection was observed in 93% of patients from the study group (vs. 92% of controls), and in 94% of patients from the study subgroup (vs. 97% of the control subgroup). The average number of biopsies revealing significant rejection was 3.4 ±1.9 in the study group (vs. 3.3 ±2.2 in the control group), and 4.0 ±2.0 in the study subgroup (vs. 3.7 ±2.2 in the control subgroup). However, the number of rejection events with haemodynamic compromise was very low – single episodes occurred in 2 patients from the study group (both patients were also enrolled in the study subgroup) and 3 patients from the control group (including 2 patients from the control subgroup). Differences were statistically non-significant.

Creatinine serum concentration at the end of the 1st hospitalization, at the end of the 1st year post-OHT, and at the end of observation were as follows: 123 ±53, 149 ±64, and 153 ±132 µmol/L in the study group (vs. 113 ±38, 150 ±51, and 147 ±53 µmol/L in the control group), and 115 ±48, 145 ±65, and 117 ±51 µmol/L in the study subgroup (vs. 111 ±44, 153 ±54, and 152 ±57 µmol/L in the control subgroup). The difference between the study and control subgroup at the end of observation was significant (p = 0.0041, Mann-Whitney U test).

Discussion

A survival benefit for OHT recipients receiving SIR was demonstrated both in the whole group of patients treated with this drug, and in the subgroup of patients receiving SIR permanently. It should be noted that this result was achieved in a group of individuals undergoing negative selection: indications to use SIR – renal function impairment, refractory rejection, transplanted heart coronary artery disease, or neoplasm – are known to correlate negatively with survival after OHT [6, 8–11]. This is in sharp contrast with the fact that there was no superior survival in prospective randomized trials with SIR undertaken in heart transplant recipients [1, 2], and some evidence of inferior results of renal graft survival in the presence of SIR [12, 13].

However, the most surprising result of our analysis is that the survival benefit comes from a decreased number of deaths unrelated to transplanted heart function. This observation led us to suspect that the typical strategy of SIR use in OHT patients, which is to decrease the number of rejection episodes and coronary vasculopathy related events with the use of SIR combined with the full dose of calcineurin inhibitors, is ineffective. The lack of a satisfactory effect of such a potent combination is presumably related to intensification of calcineurin inhibitor side effects – mostly renal impairment and hyperlipidaemia [1, 2]. The opinion that it is a justified "incidental cost" of the powerful immunosuppression is at least controversial.

Our results demonstrate that it is possible to achieve good long-term results of heart transplantation with the use of SIR and low dose CyA, despite relatively frequent occurrence of significant cellular rejection (in some patients it was an indication to introduce SIR). Despite this, biopsy-proven rejection coupled with haemodynamic compromise was extremely rare. In all prospective trials demonstrating a survival benefit as an effect of a particular medication (MMF, statins) it was achieved thanks to decreased occurrence of rejection episodes with haemodynamic deterioration [14–16]. Therefore, a paradigm to decrease the absolute number of biopsy-proven rejections, even without any signs of transplanted heart failure, is not unquestionable. However, for the majority of transplant centres it still may be difficult to accept a protocol of a prospective trial accepting a higher frequency of biopsy-proven rejection. Unfortunately, only such a study would be able to support the results of this study, obviously limited by its retrospective, non-randomized nature, and low number of participants.

Conclusion

Long-term therapy with sirolimus prolongs survival in heart transplant recipients. This effect is related to the decreased probability of non-cardiac death in this group of patients.

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