Early results of heart transplantation in the Silesian Centre for Heart Disease in the light of current recommendations

Wczesne wyniki transplantacji serca w Śląskim Centrum Chorób Serca w świetle aktualnych rekomendacji

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Abstract

Aim: The aim of the study was to assess early results of heart transplantation during the first 18 months after introduction of the new immunosuppressive protocol, suggesting preferential use of mycophenolate mofetil (MMF) instead of azathioprine, and suggesting individualization of the decision to use cyclosporine-A (CyA) or tacrolimus (TAC) as part of primary immunosuppression.
Material and Methods: Our retrospective analysis involved the results of all 53 heart transplantations performed in the Silesian Centre for Heart Disease between 1st January 2007 and 30th June 2008. Based on primary immunosuppression patients were divided into the CyA group (n=22, 51±10 y/o, 21 M/1F), and the TAC group (n=28, 38±17 y/o, 20M/8F); 3 patients did not receive any calcineurin inhibitors. We assessed overall survival, acute rejection occurrence, renal function, and infection occurrence.
Results: 1-year survival was 89%. All 6 deaths occurred during the 1st month post transplantation, and were related to a primary failure of the graft. At least one episode of significant cellular rejection (≥3A according to the ISHLT grading system) was observed in 22 patients (47%), including 10 patients from the CyA group (45%), and 12 patients from the TAC group (48%, p=0.91). Average number of rejection episodes ≥3A was 0.6±0.7 in the whole group, and was identical in number when compared between CyA and TAC groups (p=0.97). At the end of the observation none of the patients required renal replacement therapy and serum creatinine concentration was: 110±46 in the whole group, 108±29 in the CyA group, and 104±49 µmol/l in the TAC group (p=0.79). Bacterial and viral infection rate was 34 and 30% respectively in the whole group, and it was equally distributed between CyA and TAC groups.
Conclusions: Adjustment of immunosuppressive therapy to current worldwide practice allows one to achieve acceptable early survival, rate of rejection and immunosuppression-related complications.
Key words: heart transplantation, immunosuppression, cyclosporine-A, mycophenolate mofetil, tacrolimus.

Streszczenie

Celem pracy była ocena wczesnych wyników transplantacji serca wykonanych w ciągu 18 mies. od momentu wprowadzenia nowego protokołu leczenia immunosupresyjnego, w którym preferowane jest zastosowanie mykofenolanu mofetylu (MMF) w miejsce azatiopryny, a decyzja o zastosowaniu cyklosporyny (CyA) lub takrolimusu (TAC) w pierwotnym schemacie immunosupresji podejmowana jest ze wskazań indywidualnych.
Materiał i metody: Retrospektywną analizą objęto wyniki 53 transplantacji wykonanych w SCCS od 1.01.2007 do 30.06.2008 r. W oparciu o pierwotny schemat immunosupresji pacjenci zostali podzieleni na grupę CyA (n=22, 51±10 lat, 21M/1K) oraz grupę TAC (n=28, 38±17lat, 20M/8K). 3 pacjentów nie otrzymało inhibitora kalcineuryny. Oceniono przeżycie całkowite, częstość ostrego odrzucania, czynność nerek oraz występowanie zakażeń.
Wyniki: 1-roczne przeżycie wyniosło 89%. Wszystkich 6 zgonów nastąpiło w 1. miesiącu po przeszczepie i wynikało z pierwotnej niewydolności przeszczepionego serca. Co najmniej 1 epizod ostrego odrzucania komórkowego (≥3A według ISHLT) stwierdzono u 22 chorych (47%), w tym 10 chorych z grupy CyA (45%) i 12 chorych z grupy TAC (48%, p=0,91). Średnia liczba epizodów ostrego odrzucania ≥3A wyniosła w całej grupie 0,6±0,7 i była zbliżona w obu grupach (p=0,97). Na końcu obserwacji żaden z pacjentów nie wymagał leczenia nerkozastępczego, a stężenie kreatyniny wyniosło: 110±46 dla całej grupy, 108±29 w grupie CyA oraz 104±49 µmol/l w grupie TAC (p=0,79). Częstość zakażeń bakteryjnych i wirusowych wyniosła w całej grupie odpowiednio 34 i 30%, osiągając zbliżone odsetki w grupach CyA i TAC.
Wnioski: Dostosowanie protokołu immunosupresji do aktualnych wytycznych pozwala osiągnąć dobry wynik wczesny transplantacji serca, jak również akceptowalną częstość występowania ostrego odrzucania i powikłań leczenia immunosupresyjnego.
Słowa kluczowe: transplantacja serca, leczenie immunosupresyjne, cyklosporyna-A, mykofenolan mofetylu, takrolimus.

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Introduction

Many recommendations introduced recently in the field of candidate selection for heart transplantation, perioperative management of patients, and immunosuppressive strategy should positively influence early results of orthotopic heart transplantation (OHT).

Current guidelines of the International Society for Heart and Lung Transplantation (ISHLT) in the field of heart failure patient qualification for transplantation have made it easier to select a group of individuals in whom OHT is able to increase survival time substantially. In particular, a group of patients with significant and non-reversible pulmonary hypertension, with poorly controlled diabetes mellitus, or with marked obesity were neglected as candidates for transplantation [1]. Moreover, fighting early post-transplant right ventricle failure has become a cornerstone of the perioperative management of OHT recipients, thanks to use of inhaled nitric oxide and sildenafil in patients demonstrating high pulmonary vascular resistance (PVR) directly after surgery [2].

A number of large trials dealing with immunosuppression were finalized recently, and should be taken into consideration by authors of local protocols of heart transplant patient management. Mycophenolate mofetil (MMF) was proved to increase 1-year survival when compared with azathioprine (AZA) in a setting with cyclosporine-A (CyA) and corticosteroid [3]. Tacrolimus (TAC) compared with CyA (used concomitantly with AZA and corticosteroid) decreased the number of significant rejection episodes [4], and combination of TAC, MMF and corticosteroid was proved to be optimal when compared with multi-drug therapies composed of CyA, MMF and corticosteroid, and TAC, sirolimus (SIR) and corticosteroids [5]. Based on these results TAC was approved to be used as an alternative primary immunosuppressive drug instead of CyA. Monoclonal antibodies blocking receptors for interleukin-2 were shown to be an effective prophylaxis of rejection early after heart transplantation, with a safety profile superior to antithymocyte polyclonal antibodies [6-8]. Some other trials with SIR and everolimus revealed a potential benefit of mTOR (*mammalian Target Of Rapamycin*) inhibitors resulting in slowing of transplanted heart coronary artery disease progression [9, 10].

This is why the Working Group to prepare the Polish standard of immunosuppression was created under the auspices of the National Council of Transplantation, Polish Transplantation Society, and National Consultant in Clinical Transplantology with a section dedicated to heart transplantation. The standard was published and became available in 2006 [10]. There were two main points: recommendation for preferential use of MMF instead of AZA, and a suggestion to individualize the decision to use CyA or TAC as part of primary immunosuppression.

Aim

The aim of this study was to assess early results of heart transplantation during the first 18 months after introduction of the current recommendation.

Protocol of immunosuppressive therapy

Starting from the beginning of 2007, the local immunosuppressive protocol of the Silesian Centre for Heart Disease was as follows.

Triple-drug primary immunosuppressive combination was composed of CyA, MMF, and prednisone. TAC was used as a primary immunosuppressive drug in patients unable to receive oral medication within 48 hours after OHT, patients with moderate renal impairment (TAC was introduced iv. in these categories of patients), or in patients with severe hypercholesterolaemia diagnosed before OHT. Facing moderate renal impairment a decision to delay CyA introduction or start TAC iv. was dependent on risk of rejection, i.e. younger patients and females were more likely to receive TAC than older males. CyA was replaced with TAC in patients with intolerance of CyA or after the 2nd episode of significant rejection. AZA was used alternatively with MMF in patients with MMF intolerance. SIR or everolimus (EVR) replaced MMF after the 3rd episode of significant rejection or in patients with advanced coronary vasculopathy confirmed in biannual coronary angiography.

ATG or basiliximab was used in patients with acute renal failure directly after OHT. ATG was preferred in patients requiring renal replacement therapy, while basiliximab was used in patients with renal function impairment in whom we expected improvement within the 1st week after OHT. Use of ATG was also considered in patients in whom introduction of oral medication by the end of the first 48 hours after OHT was impossible (the majority of them were able to receive TAC iv.).

Target levels of immunosuppressive drugs were as follows:

1. CyA (whole blood, C_{12}, FPIA): 1st year post-OHT: 250–300 ng/mL with concomitant use of MMF, 100–150 ng/mL with SIR/EVR, or 300–400 ng/mL without MMF/SIR/EVR; 2nd and 3rd year post-OHT: 150–250 ng/mL with MMF, 50–100 ng/mL with SIR/EVR, and 200–300 ng/mL without MMF/SIR/EVR; 4th–9th year post-OHT: 100–150 ng/mL with MMF, and 150–200 ng/mL without MMF, from the 10th year post-OHT: 100–125 ng/mL;
2. TAC (whole blood, C_{12}, MEIA): 1st year post-OHT: 10–15 ng/mL; 2nd and 3rd year post-OHT: 8–10 ng/mL; from 4th year post-OHT: 6–8 ng/mL;
3. mycophenolic acid (derivative of MMF, serum, C_{12}, EMIT): 1.4–2.0 µg/mL;
4. SIR (whole blood, C_{24}, FPIA): 8–12 ng/mL with CyA/TAC, or 12–20 ng/mL without CyA/TAC;
5. EVR (whole blood, C_{12}, FPIA): 3–8 ng/mL with CyA/TAC, or 8–10 ng/mL without CyA/TAC.

Prednisone was tapered and eventually discontinued at the end of the 1st year post-OHT or later, upon elective endomyocardial biopsy results. MMF was discontinued at the end of the 3rd year post-OHT or later in patients receiving TAC. CyA or TAC was replaced with MMF at the end of the 3rd year post-OHT or later in patients receiving SIR or EVR. AZA was discontinued at the end of the 3rd year post-OHT in patients receiving TAC or at the end of the 10th year post-OHT in patients receiving CyA.

Tab. I. Characteristics of patients

	All	CyA group	TAC group	p (CyA vs. TAC)
N	53	22	28	-
sex (M/F)	44/9 (83/17%)	21/1 (95/5%)	20/8 (71/29%)	0.07
age (y)	43.8±15	50.5±10	38.1±17	**0.005**
cardiomyopathy (ischaemic/non-ischaemic)	22/31 (42/58%)	13/9 (59/41%)	7/21 (25/75%)	**0.03**
age of donor (y)	32.1±11	32.3±11	31.1±11	0.94
sex of donor (M/F)	18/35 (34/66%)	6/16 (27/73%)	12/16 (43/57%)	0.40
donor/recipients sex match (Y/N)	34/19 (64/36%)	17/5 (77/23%)	16/12 (57/43%)	0.23
ischaemic time (min)	188±51	178±50	193±51	0.24
reoperation after OHT (no./% of pts)	16 (30%)	3 (14%)	11 (39%)	0.092

Material and Methods

Our retrospective analysis was performed at the Department of Cardiac Surgery and Transplantation, Silesian Centre for Heart Disease in Zabrze, Poland, and involved all heart transplant recipients undergoing surgical procedures between 1st January 2007 and 30th June 2008. Using this criterion 53 heart transplant recipients were involved in the study.

Based on primary immunosuppression, patients were divided into the CyA group (n=22) and the TAC group (n=28); 3 patients did not receive any calcineurin inhibitors. Characteristics of patients are presented in Table I.

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 ISHLT grading system, with grade ≥3A recognized as significant, according to the working formulation published in 1990 [12].

We assessed overall survival, acute rejection occurrence, renal function and infection rate. Additionally we analyzed modifications of immunosuppressive strategy. The results are expressed as mean and/or standard deviation, or percentage when applicable. The statistical analysis was performed using Mann-Whitney U-test, and chi^2 test, respectively. Follow-up was completed on 30th June 2008.

Results

1-year survival was 89%. All 6 deaths occurred during the 1st month post transplantation, and were related to a primary failure of the transplanted graft. Heart failure was a direct cause of death in 4 cases, ischaemic stroke in 1 case, and massive bleeding from the gastrointestinal tube in 1 case. Pathology assessment excluded rejection as a cause of heart failure in all cases. In 1 patient left ventricle failure was caused by dissection of the left coronary artery, presumably related to donor chest trauma during a car accident. Three patients died before calcineurin inhibitors introduction, while the remaining 3 patients received TAC iv. A decision to use TAC was undertaken due to critical status of patients, and inability to administer immunosuppressive drugs orally. The remaining 47 patients presented excellent heart function at the end of the observation, with left ventricle ejection fraction of 56±7% (56±5 vs. 56±8 in CyA and TAC groups respectively, p=0.95).

The analysis of rejection occurrence was performed in 47 patients (22 in the CyA group, and 25 in the TAC group) who had undergone at least one procedure of endomyocardial biopsy. Of these, at least one episode of significant cellular rejection (≥3A according to the ISHLT grading system) was observed in 22 patients (47%), including 10 patients from the CyA group (45%), and 12 patients from the TAC group (48%, p=0.91). Average number of rejection episodes ≥3A was 0.6±0.7 in the whole group, and was identical in numbers when compared between CyA and TAC groups (p=0.97).

The need for haemodiafiltration occurred in 3 patients, including 2 critically ill individuals who eventually died of primary graft failure. The remaining 1 patient received TAC because of renal impairment observed from the 1st day after OHT. At the end of the observation period none of the patients required renal replacement therapy and creatinine serum concentration was normal in the majority of them (Table II). There was no difference in renal function between CyA and TAC groups.

Bacterial and viral infection occurred in 34% and 30% of patients respectively, and were equally distributed between CyA and TAC groups. Detailed information about infection is presented in Table II.

Primary immunosuppression was composed of CyA, MMF and prednisone in all 22 patients from the CyA group. 26 patients from the TAC group received a triple drug therapy comprised of TAC, MMF and prednisone. The remaining 2 pts from the TAC group received TAC with prednisone. Modifications of therapy were implemented in 3 patients (14%) from the CyA group and 9 patients (32%) from the TAC group (p=0.24).

Tab. II. Complications of immunosuppressive strategy

	All	CyA group	TAC group	p (CyA vs. TAC)
pts. requiring haemodiafiltration	3 (6%)	0	2 (7%)	0.58
serum creatinine 1 month after OHT (μmol/l)	86±32	89±21	82±39	0.42
serum creatinine at the end of observation (μmol/l)	110±46	108±29	104±49	0.79
pts. with bacterial infection requiring hospitalization	18 (34%)	8 (36%)	9 (32%)	0.99
pts. with pp65 antigen confirmed CMV infection	14 (30%)	6 (27%)	8 (32%)	0.97

In 1 patient from the CyA group CyA was replaced with TAC due to rejection. MMF was discontinued due to intolerance in 2 patients – it was replaced with AZA in 1 patient and with EVR in another patient.

MMF was discontinued due to intolerance in 4 patients from the TAC group – they remained on double drug therapy with TAC and prednisone. MMF was replaced with EVR in 3 patients receiving TAC due to rejection. In 1 patient with primary combination of TAC and prednisone it was necessary to introduce MMF due to rejection. In 1 patient, it was necessary to discontinue prednisone 3 months after OHT – she remained on double drug therapy with TAC and MMF.

Basiliximab was used in 10 patients (19%), including 1 patients from the CyA group (5%), and 8 patients from the TAC group (29%, p=0.07). The indication to use basiliximab was to delay calcineurin inhibitor introduction in 8 patients, while in 2 patients it was used electively due to increased risk of rejection (in patients on a ventricular assist device before OHT). The use of ATG took place in 1 patient from the TAC group in whom the only episode of steroid resistant rejection was treated successfully.

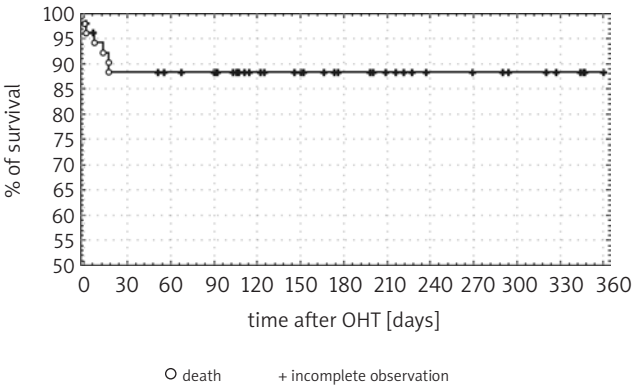

Fig. 1. Survival of patients – 1st year after heart transplantation

Discussion

Our earlier analysis performed in order to identify the main cause of early deaths in OHT recipients indicated undoubtedly right ventricle failure secondary to pulmonary hypertension as a critical complication limiting early results of transplantation in our centre [13]. As a result modifications of candidate selection and perioperative management strategy became necessary. In fact, exclusion of patients with reversibility of PVR (below the level of 2.5 Wood units) achieved at the expense of systemic resistance become a rule of the Silesian Centre for Heart Disease even before publication of this modification as part of the new ISHLT guidelines [1]. Despite this, we were even more careful selecting candidates for inhaled nitric oxide and/or sildenafil therapy among OHT recipients demonstrating right ventricle failure in the operating room, or shortly after surgery completion [2].

The main intention of the new immunosuppressive therapy protocol was to adjust the local standard to current worldwide practice in order to achieve results of treatment comparable to leading foreign centres. Some amendments were introduced even before 2007, upon availability of clinical trial results. However, a new standard prepared under the auspices of scientific and administrative authorities of the Polish Transplantation Society was an occasion to update our local protocols in a more official manner. Going into details, MMF introduction early after OHT in order to delay or decrease doses of nephrotoxic calcineurin inhibitors (instead of using cytolytic induction, which increases the risk of infection and is extremely expensive) has been common practice in our centre since 2005 [14, 15]. However, application of TAC (especially iv.) became more frequent after introduction of the new standard.

The main issue should be a comparison of heart transplantation results with official reports of international registries. The two main ones are the Registry of the International Society for Heart and Lung Transplantation (ISHLT) based mostly on results of American and West European centres, and the Scientific Registry of Transplant Recipients (SRTR) based on results of United States and Canadian centres. 1-year survival reported by ISHLT for patients undergoing heart transplantation in the last analyzed period, 2002–2005, is 86%, and SRTR reports 1-year survival of 88% in year 2005 [16, 17]. These data are comparable with 89% of 1-year survival reported in this paper. It is also worth underlining that all deaths in our report were related to primary graft failure – none of them was dependent on immunosuppressive strategy, i.e. none of them was caused by rejection, as a result of inadequate immunosuppression, or immunosuppressive therapy complications, especially infection.

The descriptive character of the analysis makes it difficult to compare different protocols of immunosuppression. It is

worth noting that the TAC-based protocol was preferentially used in a population characterized by a higher risk of rejection – younger individuals and females. Moreover, patients on TAC were at higher risk of renal failure. However, with the strategy described above we were able to achieve a satisfactory level of acute rejection occurrence and avoid renal replacement therapy in patients with perioperative renal burden. The figure of 45% of patients requiring additional therapy for significant rejection in the CyA group is very close to 44% of rejecting patients on CyA+MMF, and 48% of patients with significant rejection in the TAC group is similar to 49% of rejecting patients in the age group of 18–44 years reported by ISHLT [16].

Percentage utilization of CyA, TAC and MMF is similar to those reported by ISHLT and SRTR [16, 17]. However, the most important implication that comes from our analysis is that with careful selection of heart transplant recipients it is still justified to use CyA instead of TAC in a low-risk population, which is important in view of the current consideration to administer TAC in all heart transplant patients [18].

A number of limitations should be taken into consideration before drawing conclusions from this analysis. The nature of the study was retrospective; the decision to introduce a particular combination of immunosuppressive drugs was non-random; the study group was relatively small; and the time of observation was short. These should not interfere, however, with the most important results of this study, related to survival and rejection, which are both phenomena of the early weeks and months after heart transplantation.

Conclusion

A new protocol of immunosuppressive therapy of heart transplant patients, in accordance with new OHT candidate selection and perioperative management rules, allows one to achieve acceptable early results regarding survival, rejection rate, and occurrence of immunosuppression-related complications when compared with reports of international registries.

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