COMPARISON OF THE EFFICACY AND SAFETY OF CONSUPREN® SOLUTION AND SANDIMMUN® NEORAL SOLUTION, 50 ML IN STABLE HEART TRANSPLANT PATIENTS

Jiří Toman, Lenka Špinarová, Jan Krejčí, Petr Hude, Eva Kopečná, Vojtěch Kamarád

^a Department of Cardioangiology, Faculty hospital U sv. Anny, Brno, Czech Republic

^b Clinical Department R&D, IVAX-CR, a.s., Opava, Czech Republic, e-mail: eva_kopecna@ivax-cr.com

Received: September 22, 2002

Key words: Cyclosporine A / Transplantation of the heart / Clinical study / Comparative study Consupren vs. Sandimmun

Cyclosporine A (CyA) is a standard component of immunosuppressive regimen after heart transplantation in most centres. The widespread clinical use of cyclosporine-based immunosuppressive regimens since 1983 has led to significant improvements in the survival of cardiac allograft recipients due to decreased mortality from infections and rejections.^{1–3} CyA has been shown to be safe and effective. Owing to its success when used after the heart transplantation the number of patients has also risen. This caused growing financial demands on health insurance companies in the Czech Republic where the immunosuppressive drugs are fully reimbursed. A prospective randomized study in 11 stable heart transplant patients was performed to compare the efficacy and safety of Consupren® (IVAX-CR) a Sandimmun® Neoral (Novartis) solution based immunosuppressive regimen. The results suggest that Consupren® solution can be used as an alternative treatment to Sandimmun Neoral in CyA based regimen.

INTRODUCTION

Cyclosporine A is a cyclic polypeptide consisting of 11 amino acids. It has unique immunosuppressive properties and has been extensively used in transplant recipients in the prevention of allograft rejection or the treatment of graft-versus-host disease. Oral doses of cyclosporine vary with indication (dependent i.a. on the transplanted organ, time after the transplantation and combination with other immunosuppressants), and range from as low as 3 mg/kg/day as a maintenance dose to as high as 15 mg/kg in a single dose before solid organ transplantation.

Several therapeutic features, in addition to the marked pharmacokinetic variability, define CyA as a critical drug. Cyclosporine^{4,5}:

- displays narrow therapeutic range between ineffective and toxic drug concentrations, with the possibility of life-threatening consequences in cases of overdosing and underdosing
- shows high interindividual and intraindividual pharmacokinetic parameter variability
- displays limited and erratic gastrointestinal absorption, which is formulation dependent
- requires blood level monitoring
- shows only modest utility of body weight indexing to determine dosing

The tolerability profile of cyclosporine is characterized by a number of potentially serious adverse effects that are related to exposure, including acute or chronic nephrotoxicity, hypertension and neurotoxicity.⁶

Consupren® solution has been shown to have therapeutic activity in terms of graft survival and safety profile comparable to Novartis products. The purpose of this prospective randomized clinical study was to compare the efficacy and safety of Consupren® and Sandimmun® Neoral solution based immunosuppressive regimen in stable heart transplant patients.

MATERIAL AND METHODS

Eleven stable heart transplant patients were included in a randomized mono-center clinical study on the basis of the selection criteria. The study was approved by the State Institute for Drug Control, the local ethics committee, and each subject signed an informed consent agreement. The main criteria for enrollment were: clinically stable patients at least 6 months after transplantation, at least three stable last whole cyclosporine blood trough levels (BTL), no signs of significant infection, maintained on CyA with Azathioprine (Mycophenolate mofetil) and/or steroid immunosuppressive regimen. On the day 0 the patients were

randomized according to a randomisation scheme into two groups. The patients randomized to the Neoral group continued Neoral therapy; the patients randomized to the Consupren group were converted from Neoral to Consupren on 1:1 ratio (mg/kg/day). The dose was further adjusted to maintain target cyclosporine whole blood trough levels between 120-200 ng/ml. CyA blood levels were determined by specific RIA assay. Endomyocardial biopsy was carried out before start of the study and at the end of 12 weeks. Incidence of graft loss, graft rejection and adverse events, changes in vital signs and laboratory variables were recorded and evaluated during the period of 12 weeks after the switch.

Software and Statistical methods

Statistical analysis compared by the summary statistical methods two treatment arms of the randomized group of stable heart transplant patients. The following variables were evaluated: demography, oral daily dose of cyclosporine, number of dose adjustments, cyclosporine whole blood trough levels, incidence of adverse events, changes in vital signs and laboratory variables during the period of 12 weeks. The basic statistical parameters were calculated (mean, median, standard deviation error and percentiles). For statistical evaluation of continuous variables non-parametric Mann-Whitney U test was used. For evaluation of categorical variables M-L a Chi-square test was used ($P = 0.05$).

RESULTS

Eleven patients were enrolled and completed the whole study period, 5 patients were enrolled in the Consupren group and 6 patients in the Neoral group. There were 9 men and 2 women, mean age of 50.5 ± 10.6 (range 33 to 68 years), mean weight 87.4 ± 17.6 (range 57 to 110 kg), 100 % were Caucasian. The main characteristics of the group are summarized in Tab. 1.

No rejection episode was diagnosed 12 weeks after the switch in both groups. Patient and graft survivals were 100%. The mean CyA whole blood trough concentration at the start of the study was 163.4 ng/ml in Consupren group vs. Neoral group 156.8 ng/ml, and at the end 196.2 ng/ml in the Consupren group and 148.0 ng/ml in the Neoral group (Tab. 2+3). Mean CyA doses were stable during the whole period. Mean dose of CyA at the start was 237 mg/day in Consupren group vs. 220 mg/day in the Neoral group, and at the end in the Consupren group 226 mg/day vs. 216.7 mg/day in the Neoral group (Tab. 4+5, Graph 1). The dose of cyclosporine had to be changed 11 times (25 %) in both groups, 4× in Neoral group and 7 times in Consupren group (Graph 2).

There was no difference in the key comparative clinical parameters. Blood pressure increased slightly in the Consupren group from systolic 133 ± 12 mmHg at the start to 147 ± 15.2 mmHg at the end, and from diastolic 88.8 ± 11.5 mmHg at the start to 92.0 ± 15.2 mmHg

Table 1.

MAIN CHARACTERISTICS OF THE STUDY GROUP			
Parametr	Study arm		
	Sandimmun® Neoral	Consupren®	Total
Number of patients	6	5	11
Recruitment	9/1999–2/2000	9/1999–12/1999	9/1999–2/2000
Women	2 (33%)	0 (0%)	2 (18%)
Men	4 (67%)	5 (100%)	9 (82%)
Age			
Mean (SD)	51.2 (12.0)	49.8 (10.0)	50.5 (10.6)
Median	53	55	54
Min	36	33	33
Max	68	57	68
Indication for transplantation			
Ischemic heart disease	2 (33%)	3 (60%)	5 (45%)
Dilative cardiomyopathy	4 (67%)	2 (40%)	6 (55%)

Table 2.

CYCLOSPORINE WHOLE BLOOD TROUGH LEVELS AT STUDY START [ng/ml]						
Group	N	Mean ¹	SD	Median	Min	Max
CONSUPREN®	5	163.4 ^A	20.7	161.0	145	198
SANDIMMUN® NEORAL	6	156.8 ^A	24.1	164.5	120	179
Total	11	159.8	21.8	161.0	120	198

¹⁾ The is no significant difference between the values in the columns with the same apostrophe ($P < 0.05$)

Table 3.

CYCLOSPORINE WHOLE BLOOD TROUGH LEVELS AT STUDY START [ng/ml]						
Group	N	Mean ¹	SD	Median	Min	Max
CONSUPREN®	5	163.4 ^A	20.7	161.0	145	198
SANDIMMUN® NEORAL	6	156.8 ^A	24.1	164.5	120	179
Total	11	159.8	21.8	161.0	120	198

¹⁾ The is no significant difference between the values in the columns with the same apostrophe ($P < 0.05$)

Table 4.

CYCLOSPORINE WHOLE BLOOD TROUGH LEVELS AT STUDY END [ng/ml]						
Group	N	Mean ¹	SD	Median	Min	Max
CONSUPREN®	5	196.2 ^A	88.5	172.0	140	352
SANDIMMUN® NEORAL	6	148.0 ^A	34.3	141.5	114	205
Total	11	169.9	66	158.0	114	352

¹⁾ The is no significant difference between the values in the columns with the same apostrophe ($P < 0.05$)

Table 5.

CYCLOSPORINE DOSAGE AT STUDY END [mg/day]						
Group	N	Mean ¹	SD	Median	Min	Max
CONSUPREN®	5	226.0 ^A	57.3	240.0	140	280
SANDIMMUN® NEORAL	6	216.7 ^A	58.5	230.0	110	280
Total	11	220.9	55.2	230.0	110	280

¹⁾ The is no significant difference between the values in the columns with the same apostrophe ($P < 0.05$)

Graph 2.

CYCLOSPORINE DOSAGE (n = 11)

WHOLE CYCLOSPORINE BLOOD TROUGH LEVELS (n = 11)

Graph 1. Dosage and cyclosporine whole blood trough levels

at the end. Systolic and diastolic blood pressure in Neoral group remained unchanged during the entire period. In the study the test drug was very well tolerated. Incidence of adverse events and changes in laboratory variables during the period of 12 weeks after the switch were comparable. Only one new adverse effect was recorded (Herpes zoster) in the Consupren group and this disappeared 17 days after appropriate treatment. The laboratory results of creatinine, urea, liver enzymes, uric acid, glycemia, cholesterol, triglycerides, mineral levels and red and white blood counts remained unchanged during the entire study period in both arms. Leucopenia, thrombocytopenia, slightly increased cholesterol, TG, urea, creatinine, and uric acid were the most common laboratory abnormalities in both arms.

CONCLUSION AND DISCUSSION

The number of enrolled patients was relatively low. The recruitment of the patients was influenced by specific indication with limited number of eligible patients. Since 1993 there have been 170 heart transplanted patients in the Cardiovascular and transplantation center in Brno, 125 out of them still living in 2001 and controlled by the center. The patient survival in Brno cardioangiological center is about 80% after one year and 69% after three years.⁷

Mean dosage of cyclosporine in stable heart transplant patients ranged in several studies from 3.3–3.6 mg/kg/day⁸. In our study the mean dose of cyclosporine was slightly lower (2.7 mg/kg/day) and was influenced by other immunosuppressive drugs given in a combination regimen and by the centre's experience. Increase in blood pressure in Consupren group can be explained by the higher cyclosporine exposure (higher mean BTL in Consupren group at the study end 196.2 vs. 147 ng/ml in Neoral). Other parameters were fully comparable.

Although the study group is rather small for appropriate statistical evaluation, the results suggest that Consupren[®] can be used as an alternative cost-effective treatment to Sandimmun[®] Neoral in CsA based regimens in stable renal transplant recipients.

ACKNOWLEDGEMENT

The authors would like to thank to Mr. Svobodník, Center of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic for statistical evaluation.

REFERENCES

1. Oyer PE, Stinson EB, Jamieson SW (1983). Cyclosporine in Cardiac Transplantation: a 21/2 year follow-up. *Transplant Proceedings*; 15(suppl 1), 2546.
2. Eisen HJ, Hobbs RE, Davis SF, Laufer G, Mancini DM, Renlund DG, Valantine H, Ventura H, Vachieri JL, Bourge RC, Canver CC, Carrier M, Constanzo MR, Copeland J, Dureau G, Frazier OH, Dorent R, Hauptman PJ, Kells C, Master R, Michaud JL, Paradis I, Smith A, Vanhaecke J (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 (5), 663–671.
3. Micromedex database, Volume 2002.
4. Foulds D, Goa KL, Benfield P (1993) Cyclosporine. A Review of its Pharmacokinetic Properties, and Therapeutic Use in Immunoregulatory Disorders. *Drugs*; 45(6), 953–1040.
5. Sadeg N, Pham-Huy C, Rucay P, Righenzi S, Halle-Pannenko O, Claude JR, Bismuth H, Duc HT (1993) In Vitro and in Vivo Comparative Studies on Immunosuppressive Properties of Cyclosporines A, C, D and metabolites M1, M17 and M21. *Immunopharmacol. Immunotox.*; 15(23), 163–177.
6. Lucini D, Milani RV, Ventura HO, Mehra MR, Messerli FH, Murgo JP, Regenstein F, Copley B, Malliani A, Pagani M (1997) Cyclosporine-Induced Hypertension: Evidence for Maintained Baroreflex Circulatory Control. *Journal Heart and Lung Transplantation*; 16(6), 615–620.
7. Krejci J, Hude P, Spinarova L, Toman J, Cerny J, Nemec P, Frelich M, Sirotkova A (2000) Transplantace srdce – indikace, komplikace, terapie – naše zkušenosti ze sledování 100 pacientů po srdeční transplantaci. *Vnitřní lékařství*; 46 (11), 750–755.
8. Dunn ChJ, Wagstaff AJ, Perry CM, Plosker GL, Karen LG (2001) An Updated Review of the Pharmacokinetic Properties, Clinical Efficacy and Tolerability of a Microemulsion-Based Formulation (Neoral[®]) in Organ Transplantation. *Drugs*; 61(13), 1959–2016.