Short Communication
Volume 11:5, 2021

Journal of
Transplantation Technologies & Research

ISSN: 2161-0991 Open Access

Pediatric and Congenital Heart Disease Patients by the American Heart Association

Yoshiki Sawa*

Department of Cardiovascular Surgery, Addis Ababa Science and Technology University, Ethiopia

Short Communication

The aim of our work is to study the effect of MSCs on the rejection control of solid organ transplantation on a preclinical model of heterotopic heart-lung transplantation in rats. This experimental model investigated the effect of intravenous MSC infusion and compared it with immunosuppression induced by Cyclosporine A (CyA). In this study male Wistar rats were utilized as the heart and bone marrow donors, and male Sprague-Dawley rats as the recipients [1]. They weighed between 250 and 275 g. The animals were purchased from Charles River Laboratories, Italy, fed standard rodent chow (Rieper, Italy) and water both given ad libitum under a 12 h light/dark cycle. All the animal procedures were carried out with the approval of the University of Pisa's Ethical Committee for Animal Use and Care. To evaluate the grade of rejection in this model, histological analysis was performed on the heart and lung allografts harvested 5 days after transplantation [2]. Our results were expressed according to Billingham's standardized working formulation for heart and lung rejection. We found that the heart rejection grade of the control group was uniform and classifiable as the histology revealed the presence of diffuse small lymphocyte infiltrates with myocytic damage and perivascular edema. Both the treatments with CyA and MSC infusion caused a reduction of acute rejection to 2B.

Lung histological analysis showed similar results to that for the heart. The lung lobe, without breathing function, acts as a blood reservoir and in the space of a few days undergoes complete hepatization [3]. In the control group, the mean grade of rejection was with the presence of diffuse perivascular, interstitial and alveolar infiltration composed by mononuclear cells; prominent pneumocyte damage and neutrophils infiltration were also present. Necrotizing vasculitis and endobronchial exutation were evident. In the group of animals treated with CyA there was a reduction to the A2/ A3 level. The histological evaluation showed a perivascular mononuclear infiltrate and expansion of the perivascular interstitium by inflammatory cells. Alveolar macrophage desquamation was also present. Both immunosuppression with MSC infusion and the combined therapy (MSCs + CyA) reduced the rejection level to A2 compared to the controls [4]. The treatment with MSCs resulted in high variability and consequently the reduction was not statistically significant. The histology evidenced scattered mononuclear infiltrates and blood vessels cuffed by plasmacytoid cells MSCs have immunomodulatory effects and interact with the immune system. Because of these effects they are considered a promising option for the future development of clinical applications such as transplantation, in view of their role as immunosuppressants. Although the immunomodulatory effect of MSCs in vitro is well established, recent works have yielded conflicting results in in vivo studies on preclinical organ transplantation models. In this work we studied the ability of MSCs to reduce acute rejection, either on their own or in combination with Cyclosporine A, in a model of heterotopic heart-lung transplantation [5]. These results are in contrast with the findings of Inoue, who reported that MSCs were not only ineffective in prolonging graft survival, but also that when they were administered in combination with CyA graft rejection was accelerated. It is important to underline that the protocols used by Inoue differed from ours. Indeed, a higher dose of MSCs was injected systemically in our experiments, while Inoue's group used lower doses. Moreover, in the combined treatment we used a ten-fold higher dose of CyA (5 mg/kg), administered daily and beginning with the first dose 24 hours before transplantation, versus 0.5 mg/kg from day 5 to 9 in Inoue's protocol.

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***Address for Correspondence:** Yoshiki S, Department of Cardiovascular Surgery, Addis Ababa Science and Technology University, Ethiopia, E-mail: sawap@surg1medosaka-u.ac.jp*

Received 06 September 2021; **Accepted** 20 September 2021; **Published** 27 September 2021

How to cite this article: Yoshiki Sawa. "Pediatric and Congenital Heart Disease Patients by the American Heart Association." *J Transplant Technol Res* 11 (2021): 191.