HEART FAILURE AND TRANSPLANTATION
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Tarun W. Dasari, MD, MPH
University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
USA
Tarun-Dasari@ouhsc.edu

Nandini Nair, MD, PhD
Providence Sacred Heart Medical Center
Spokane, Washington
USA
Nandini.nair@gmail.com

REVIEWS:

Mortensen SA, et. al. The Effect of Coenzyme Q10 on Morbidity and Mortality in Chronic Heart Failure Results From Q-SYMBIO: A Randomized Double-Blind Trial. J Am Coll Cardiol HF 2014; 2:641–9

Heart failure (HF) is a complex condition secondary to multiple pathophysiologic processes. Data on the beneficial effects of nutritional supplements in HF is sparse. One such supplement is Coenzyme Q10 (CoQ10). The benefits of CoQ10 in HF were studied by Mortensen et al. in this issue of JACC: HF.

Q-SYMBIO is a two-year, multicenter, international, double blind randomized clinical trial of NYHA III/IV chronic HF patients with reduced ejection fraction. The study had two phases. The first phase was a short-term (16 weeks) evaluation of the impact on CoQ10 on NYHA functional class, 6-minute walk distance, echocardiography parameters (LVEF and LV dimensions) and change in NTpro-BNP levels. The long-term phase evaluated the impact on major adverse cardiovascular events (worsening HF, cardiovascular death, mechanical assist device implantation or urgent cardiac transplantation).

A total of 420 patients were enrolled, of which 202 received CoQ10 (100 mg three times a day) and 218 patients received placebo. Serum CoQ10 and NTpro-BNP levels were measured in all patients. An intention to treat analysis was used, and clinical outcomes were assessed during the follow-up of 106 weeks. Baseline characteristics were similar between the two groups. The majority of patients were on standard HF therapy (90% received ACEi/ARB's and 72-76% received beta-blockers) and had NYHA class III symptoms (87-88%). Baseline LVEF was similar in both groups (31%).

During the short-term follow-up, there were no significant differences noted in NYHA functional class, 6-minute walk distance and NTpro-BNP levels. The level of serum CoQ10 at week 16 increased significantly to about 3 times the baseline value in the CoQ10-treated group. During the long-term follow-up, a total of 87 patients had reached the primary endpoint (adverse cardiac events), and 60 patients had died. There was a significantly lower incidence of major adverse cardiovascular events in the CoQ10 group (15%) compared to the placebo group (26%) (HR: 0.50, CI: 0.32 to 0.80; p=0.003). The following secondary endpoints were significantly lower in the CoQ10 group compared with the placebo group: cardiovascular mortality (9% vs.16%, p=0.039), all-cause mortality (10% vs. 18%, p=0.036), and incidence of hospital stays for HF (8% vs. 14%, p=0.033). In addition, a significant improvement in NYHA functional class was noted in the CoQ10 group (p=0.028). However there were no differences noted in echocardiographic parameters and NTpro-BNP levels during the follow-up. CoQ10 was well tolerated with no significant adverse events.

This interesting study demonstrates the utility of a popular nutritional supplement, CoQ10 in patients with NYHA Class III/IV HF. The last decade has seen very limited development in medical therapies that have had significant impact on cardiovascular mortality and morbidity in HF. Recently, Neprilysin shot into limelight as

the next weapon in our armamentarium of HF therapies with a significant reduction in mortality. Owing to complex and diverse pathophysiologic pathways, the treatment for HF can be challenging. Hence the demonstration of improved survival with a relatively safe and inexpensive nutritional supplement is very promising. The postulated restoration of CoQ10 in HF patients, who supposedly have depleted levels, may have a direct impact on some key cellular pathways including, but not limited to, mitochondrial oxidative phosphorylation, stabilization of mitochondrial permeability, antioxidant potentiation, and improved cellular energetics and endothelial function. This study is also unique in that it demonstrated significant improvement in hard clinical endpoints as opposed to surrogate markers of disease and a much robust reduction in mortality in an advanced HF cohort (mainly NYHA III class) compared to Neprilysin (PARADIGM HF study). Before a widespread adoption of CoQ10 by the HF and medical community, these results need to be carefully replicated in US in a larger and a more diverse population of HF subjects. If reproduced, this may pave the way for the adoption of an inexpensive and safe therapy that will supplement the already available potent drug therapy in HF. Carefully designed studies need to be conducted to test other potential applications of this supplement in the field of cardiovascular medicine.

Singh K et. al. "Superiority of Rapamycin Over Tacrolimus in Preserving Non-human Primate Treg Half-Life and Phenotype After Adoptive Transfer." Am J Transplant 2014; 14: 2691-2703

As organ transplantation still remains the gold standard for end stage organ failure and the drive to resolve ongoing challenges of immune suppression continue, use of cellular therapy for inducing tolerance appears to be an attractive option. Regulatory T cells (Tregs) have an important role in inducing tolerance in transplant recipients. Treg- mediated tolerance to transplant antigens is highly specific, localized, and is involved in controlling responses mediated by CD4+, CD8+ T cells, natural killer (NK) cells, B cells, as well as other antigen-presenting cells. Tregs have the distinct advantage of being capable of utilizing different immunosuppressive mechanisms suitable for different microenvironments. Being antigen specific and adaptable, Tregs can selectively target graft tissues. Tregs have therefore risen in prominence as cellular therapeutic agents. To achieve success in clinical trials on Treg therapy, critical data are required such as determining the effective dosage, specificity and the influence of adjunct immunosuppression therapy.

In this issue of American Journal of Transplantation, Singh et al. characterize the behavior of Tregs in the primate system using a non human primate model (rhesus macaques). The paper tries to address questions in cellular therapy in the murine system which need to be extrapolated into primates and humans. Singh et al. have investigated some of the basic problems in translating the murine data into clinical practice with a focus on dose, delivery, and stability of Tregs, post infusion, as well as their interactions with concomitant immunosuppressive agents. As these studies are challenging to perform in patients, the development and use of a non-human primate models seem attractive.

The objectives of the study were to 1) determine the primate pool of Tregs and the pharmacokinetics, 2) determine the optimal dosing of Tregs, 3) study the distribution of the infused Tregs and 4) assess the impact of immunosuppression (Tacrolimus and Rapamycin) on the expression and survival of the infused Tregs.

The authors used juvenile rhesus monkeys as a non-human primate model in this study. CD4+CD25++cD127-/low putative Tregs were isolated from these animals. They were expanded, stimulated with anti-CD3/CD28-coated micro beads and pulsed with rapamycin for 48 h following which they were harvested, washed and cryopreserved. Tregs were labeled with CFSE (5,6-carboxy fluorescein diacetate succinimidyl ester), washed, and cultured for 24 hours to reduce the toxic effects of CFSE prior to infusion into recipients (rhesus macaques). Flow cytometry was used for cell analysis. The phenotype of the expanded Tregs was analyzed for expression of CD3, CD4, CD25, CD127 and FoxP3. Rapamycin and tacrolimus were administered to animals to reach trough levels of 5-15 ng/mU and 8-12 ng/mU, respectively, 2 weeks ahead of Treg infusion and was continued through the length of the analysis.

The results of this study provide some important observations that may pave the way for critical advances in cellular therapy in solid organ transplantation. Using CFSE-labeled Tregs, the accessible pool was calculated, and their survival kinetics was determined. The Treg pool derived was much higher than expected in the human system. The discrepancy was attributed to differences in the species. Dose response curves for Tregs were generated for the first time in primates. Determination of cell survival kinetics is important for adequate cell dosing. Hence half-life of infused cells and their stability were studied. A biphasic elimination pattern was noted suggestive of two different subpopulations. One group was distributed and eliminated early while another subpopulation demonstrated a longer half-life. Interestingly infused cells were found to migrate to the lymph nodes and bone marrow. The pattern of elimination was similar to that observed in peripheral blood. Tregs were considered phenotypically stable if they continued to express CD25 and FOXP3. By post infusion day 16, <30 % of the infused Tregs were CD25+/FOXP3+. The impact of concurrent immunosuppression therapy in cell stability was then studied. Interesting changes in phenotype were noted in animals receiving no immunosuppression versus those treated with tacrolimus or rapamycin. With no immunosuppression, the infused Tregs rapidly lost expression of FoxP3 and CD25 markers. Tacrolimus treatment preserved CD25 expression and the longevity but not FoxP3 expression while rapamycin treatment preserved both CD25+ and FOXP3+. The rapamycin effect was also noted in the bone marrow and lymph nodes. The underlying mechanism for this effect is unknown, but the author postulate a better immunosuppressive profile of Rapamycin.

This paper addresses some cardinal principles in cell-based therapies. The availability of a non-human primate model to perform the pre-clinical experiments would lend incredible opportunities to simulate the human system as cell based drug therapy evolves. Though several questions remain, in terms of optimal cell dosing and tracking in human systems and their survival post infusion, the observations made by Singh et. al. will have significant impact on the design of clinical trials and the standardization of conditions for manufacturing Tregs for human use. The role of concomitant immunosuppression therapy on the survival of Tregs will help design effective cell based therapies for rejection.

ARTICLES OF INTEREST:

JACC Heart Failure:

Kolb C, Sturmer M, Sick P, et al. Reduced risk for inappropriate implantable cardioverter-defibrillator shocks with dual-chamber therapy compared with single-chamber therapy: results of the randomized OPTION study. JACC Heart failure 2014;2:611-9.

European Journal of Heart Failure:

Saberniak J, Hasselberg NE, Borgquist R, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. European journal of heart failure 2014;16:1337-44.

Duncker D, Haghikia A, Konig T, et al. Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function-value of the wearable cardioverter/defibrillator. European journal of heart failure 2014;16:1331-6.

Journal of Cardiac Failure:

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Collste O, Alam M, Sundqvist M, et al. Vulnerability to sympathetic stress does not persist in takotsubo stress cardiomyopathy. Journal of cardiac failure 2014;20:968-72.

New England Journal Of Medicine:

Ubel, PA. Transplantation Traffic — Geography as Destiny for Transplant Candidates. New England Journal of Medicine 2014; 371:2450-2452. (Perspective)

American Journal of Transplant:

•Singh K et al. Superiority of Rapamycin Over Tacrolimus in Preserving Non-human Primate Treg Half-Life and Phenotype After Adoptive Transfer. Am J Transplant 2014 ;14: 2691-2703.

Q Tang. Pharmacokinetics of Therapeutic Tregs. Am J Transplant 2014 ;14: 2679–2680. (Editorial)

Glanville AR. CLAD: Does the Emperor Have New Clothes? Am J Transplant 2014 ;14: 2681-2682. (Editorial)

Krummey SM, Ford ML. Braking Bad: Novel Mechanisms of CTLA-4 Inhibition of T Cell Responses. Am J Transplant 2014 ;14: 2685–2690. (Minireview)

Journal Of Heart and Lung Transplantation:

Lund LH, Gabrielsen A. Biomarkers in advanced heart failure—pathophysiology leading to clinical use? J Heart Lung Transplant 2014; 33:1213-1214 (Editorial Commentary)

Pronschinske KB et al. Neutrophil gelatinase-associated lipocalin and cystatin C for the prediction of clinical events in patients with advanced heart failure and after ventricular assist device placement. J Heart Lung Transplant 2014; 33:1215-1222.

Cornwell WK et al. Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. J Heart Lung Transplant 2014; 33:1295-1303.

Tallaj JA et al. Have risk factors for mortality after heart transplantation changed over time? Insights from 19 years of Cardiac Transplant Research Database study. J Heart Lung Transplant 2014; 33:1304-1311.