S6_5

# Targeting Macrophage Subsets to Attenuate Cardiac Remodeling and Dysfunction after Experimental Myocarditis in Rat

**Shunit Rinkevich-Shop**, Tamar Ben Mordechai, David Kain, Micha S. Feinberg, Natalie Landa-Rouben, Jonathan Leor
*Cardiovascular Research Institute, Tel-Aviv University, Sheba Medical Center, Israel*

**Background:**
Myocarditis is a life-threatening inflammatory heart disease. Cells of the monocyte and macrophage lineages comprise the majority of infiltrates in experimental myocarditis. Thus, we aimed to determine the role of macrophage subsets in the pathogenesis and progression of myocarditis, and to test the hypothesis that targeting macrophages would modulate disease progression and outcome.

**Methods and Results:**
Experimental autoimmune myocarditis (EAM) was induced in 67 Lewis rats. 27 of them were sacrificed at different time points to assessM1 and M2- macrophage subsets by flow cytometry. The remaining rats were randomized and subjected to either early macrophage depletion (from day 8-14 after EAM induction) by intravenous injection of clodronate-liposomes (CL) or PBS-liposome injections, or late depletion (from day 15-35 after induction of EAM). Left ventricular (LV) remodeling and function were evaluated by three echocardiography studies; before induction of EAM, before CL treatment, and 35 days after induction of EAM. Macrophagesin the heart peaked at 21 days after induction of EAM (25±7%,p=0.0008).The number ofM1 macrophages in the heart was highest at 14 days after EAM induction (16.3±2%). Subsequently, M2 macrophages peaked at day 21 (15.5±2.7%, p=0.003). Early macrophage depletion decreased LV diastolic dimension and volume by 5.3±3.9% and 10.4±8% (p=0.04), by serial echocardiography studies. Latemacrophage depletion increased LV wall thickness and decreased LV systolic dimension and volume by10.2±4%and 21±8%(p=0.03). Significantly, late macrophage depletion increased LV ejection fraction and fractional shortening 35 days after EAM.

**Conclusions:**
Our study describes, for the first time, the kinetic of M1 and M2 macrophages after myocarditis and shows that macrophages contribute to the progression of remodeling and dysfunction. Thus, targeting macrophages could be a new therapeutic strategy to improve cardiac remodeling and function in myocarditis.