Potential of Regenerative Therapy with Medical Assist Devices

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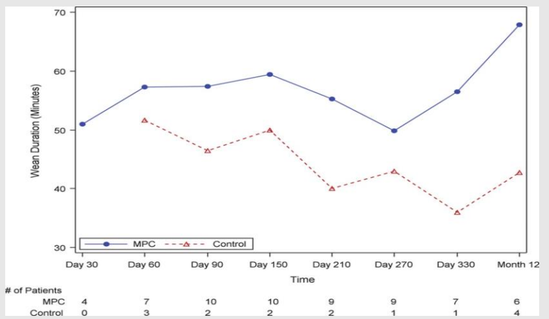
Cell Therapy for Heart Failure

Heart failure continues to be the leading cause of morbidity and mortality not only in the United States but throughout the world. Despite advances in medical and device therapy, many patients continue to have significant symptoms leaving heart transplantation, left ventricular assist devices (LVAD), or palliative care as the only options. This has stimulated interest in regenerative therapies including stem cell therapy. Based on positive preclinical results, the initial clinical trials used predominantly autologous bone marrow mononuclear stem cells (BMC). Trials with BMC demonstrated excellent safety but only modest efficacy most likely due to the significant variability with autologous BMC which is related to the decline in the number and potency of stem cells with age and cardiac risk factors.

This has stimulated the next generation of cell therapies which include allogeneic cells, cardiac derived cells, and enhanced cultured autologous cells. A recent large double-blind, placebo controlled Phase 2 trial using enhanced BMC cells (IxCell-DCM) demonstrated a significant reduction in mortality and cardiovascular hospitalizations in cell-treated patients. A second large Phase 2 trial using enhanced mesenchymal stem cells (MSCs) will be presented at ESC and a large Phase 3 trial with allogeneic MSCs is underway.

LVAD + MSC Circulation 2014; 129(22):2287-96.

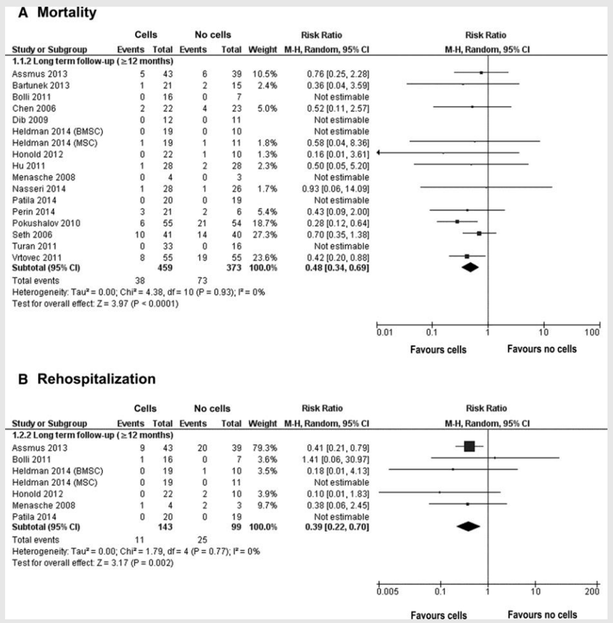


Mechanical Support & Cell Therapy

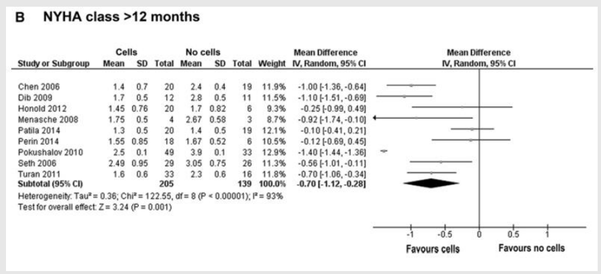
An even more attractive idea is to combine the benefits of novel, mechanical left ventricular support devices with regenerative therapy. To date, there have been a total of 67 patients randomized in 11 published clinical trials with the combination of cell therapy and LVAD trials. The largest of these (N=30) was an NIH-sponsored trial using allogeneic MSCs which demonstrated a potential benefit in LVAD weaning and a suggestion of mortality benefit.

In summary, despite optimal medical and device therapy the number of patients with advanced HF continues to grow. Both novel mechanical assist devices and regenerative therapy represent potential solutions. The combination of these two unique therapies may be a particularly attractive solution.

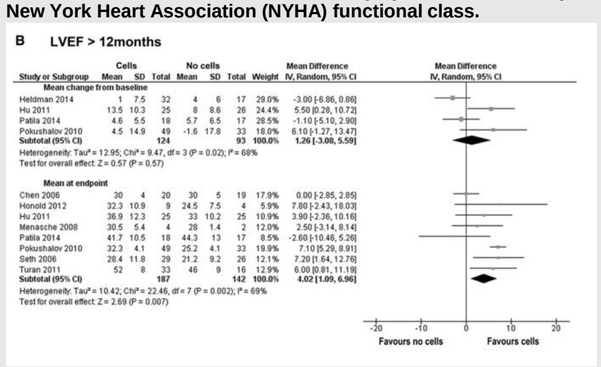
Fisher Meta-Analysis Circulation Research. 2015; 116: 1361-1377



Effect of cell treatment on primary outcomes during long-term follow-up (≥12 months).



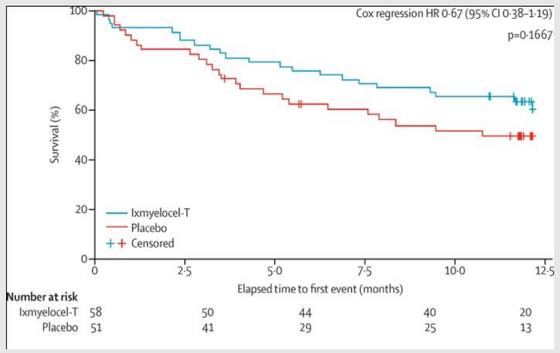
Effect of cell treatment on heart failure symptoms measured by New York Heart Association (NYHA) functional class.



Changes in left ventricular ejection fraction (LVEF) after cell treatment compared with control.

IxCell-DCM Lancet. 2016;387(10036):2412-21.

	Primary endpoint without investigational product procedure related events		Sensitivity endpoint with investigational product procedure related events	
	Placebo (n=51)	Ixmyelocel-T (n=58)	Placebo (n=51)	Ixmyelocel-T (n=58)
Rate ratio (95% CI)	..	0·62 (0·42–0·97)	..	0·62 (0·41–0·95)
p value	..	0·0344	..	0·0267
Events per 100 patient-years	109·97	67·96	112·17	69·26
Patient-years exposed	45·5	54·5	45·5	54·5
Total events	50	38	51	38
Distribution of events by patient				
0	26 (51%)	36 (62%)	25 (49%)	36 (62%)
≥1	25 (49%)	22 (38%)	26 (51%)	22 (38%)
1	9 (18%)	13 (22%)	10 (20%)	13 (22%)
2	11 (22%)	3 (5%)	11 (22%)	3 (5%)
3	2 (4%)	5 (9%)	2 (4%)	5 (9%)
4	2 (4%)	1 (2%)	2 (4%)	1 (2%)
5	1 (2%)	0	1 (2%)	0
Death (n patients)	7 (14%)	2 (3%)	..	..
LVAD insertion (n patients)	0	3 (5%)	..	..
Heart transplant (n patients)	1 (2%)	1 (2%)	..	..
Cardiovascular admissions to hospital (n patients)	24 (47%)	22 (38%)	..	..
Unplanned outpatient or emergency department visit (n patients)	0	2 (3%)	..	..



Combined Cell therapy + LVAD

Study	N	Etiology	LVAD	Cell Type	Delivery	Recovery*	Death	Arrhythmia (count)
Pagani (2003)[36]	5	ICM	-	Autologous SkM	Intramyocardial	0	1	AF (2), sVT (2)
Dib (2005)[39]	6	ICM	-	Autologous SkM	Epicardial	0	3	sVT (1), VF (1)
Fujita (2011)[42]	4	ICM	Pulsatile	Autologous SkM	Intramyocardial	1	4	VBP (-)
Sawa (2012)[41]	1	NICM	Pulsatile	Autologous SkM	Epicardial Sheet	1	0	0
Miyagawa (2009)[43]	1	ICM	Pulsatile	Autologous BMMC + SkM	Intramyocardial	0	1	0
Nasseri (2007)[45]	10	NICM	Pulsatile (2), Continuous (8)	Autologous BMMC	Intramyocardial	1	2	-
Gojo (2007)[44]	1	ICM	Pulsatile	Autologous BMMC	Intracoronary	1	0	-
Anastasiadis (2011)[37]	2	ICM	Continuous	Autologous BMMC	Intramyocardial	0	0	-
Anastasiadis (2012)[38]	1	ICM	Continuous	Autologous BMMC	Intramyocardial	0	0	-
Ascheim (2014)[40]	20	ICM (13) NICM (7)	Continuous	Allogeneic MSC	Intramyocardial	0	0	0
Stempien-Otero (2015)[55]	6	ICM	Continuous	BMMC $CD34^+$ $CD34^-$	Intramyocardial	0	0	Ventricular arrhythmias (4)
Total	57					4	11	10