Reduction in Ventricular Arrhythmias with Ixmyelocel-T: Results from the IxCell-DCM Trial

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Abstract

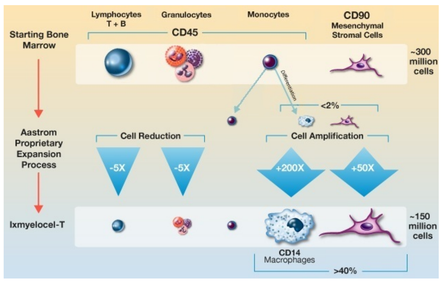
Background: Ixmyelocel-T is an investigational multicellular therapy produced from a person's own bone marrow by selectively expanding two key types of bone marrow mononuclear cells: CD90+ mesenchymal stem cells and CD45+ CD14+ autoflourescent+ alternatively activated macrophages. IxCELL-DCM (N=109) was a double blind, placebo controlled trial that randomized NYHA class III or IV participants (hereafter referred to as patients) with LVEF≤35%, and either 6 minute walk ≤400 meters, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) ≥2000 pg/ml, or BNP ≥400 pg/ml within 30 days of screening, or HF-related hospitalization or unscheduled outpatient or emergency department visit within the last 6 months 1:1 to intramyocardial ixmyelocel-T:placebo. Treatment with ixmyelocel-T resulted in a 37% reduction in the primary endpoint of all-cause mortality, cardiac hospitalizations, and unplanned outpatient treatment of acute decompensated HF at 1 year (p=0.0344). Multiple mechanisms have been proposed for how ixmyelocel-T may reduce cardiac events, but the exact mechanism(s) remains unclear.

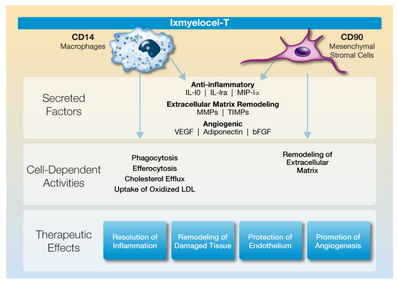
Methods: A pre-specified secondary endpoint included intermittent assessment of AICD interrogation for events defined as ventricular arrhythmia lasting > 30 sec, ventricular tachycardia resulting in shock, and any ventricular arrhythmia resulting in anti-tachycardia pacing. 58/58 ixmyelocel-T patients and 50/51 placebo patients had AICD interrogation during the 12 month follow-up. A Poisson regression of the events per 100 patient years was performed (Wald Chi-Square).

Results: Patients randomized to ixmyelocel-T had an average of 236.42 ventricular arrhythmia events/ 100 patient years compared to 310.99 in the placebo group (p=0.0502), rate ratio of 0.76 (0.58-1.00, 95% CI). Moreover, 8 patients who received placebo had SAEs of ventricular fibrillation compared to none in the patients who received ixmyelocel-T.

Discussion: These data suggest that reduction in ventricular arrhythmias may play a role in the clinical benefit observed with ixmyelocel-T multicellular therapy.

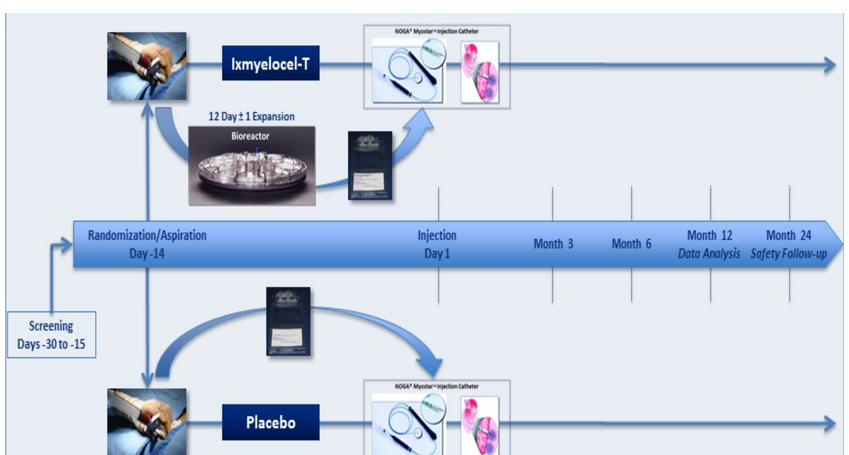
Ixmyelocel-T: Composition





Ixmyelocel-T is a multicellular therapy generated from patient's bone marrow mononuclear cells . The process used to generate ixmyelocel-T expands the CD90+ mesenchymal stromal cells and CD14+ monocytes and M2-like macrophages while retaining many of the CD45+ cells found in the bone marrow. Ixmyelocel-T produces anti-inflammatory and angiogenic factors useful for cardiac repair despite the advanced age of the patient and the systemic disease state. This mixture of cells may address the underlying disease process to promote tissue repair and recovery.

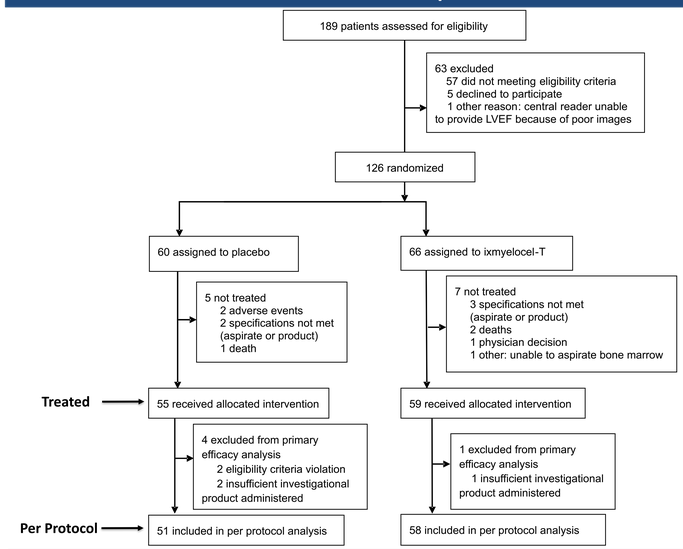
ixCELL DCM: Double Blind Placebo Controlled Trial



Patient Population

Category		Placebo (N=51)	Ixmyelocel-T (N=58)	P value
Demographics				
Sex (%)	Male	88%	95%	0.30
Age (years)	Mean	64.7	65.3	0.69
Race (%)	White	88%	91%	0.75
Risk Factors				
Hypertension	%	90%	81%	0.28
Hyperlipidemia	%	96%	97%	1.00
Diabetes	%	51%	41%	0.34
CV Medical History				
Previous CABG	%	63%	55%	0.44
Previous PCI	%	82%	85%	0.80
Previous MI	%	96%	88%	0.17
AICD	%	96%	93%	0.68
CRT	%	39%	50%	0.33
Baseline				
NYHA Class III	%	92%	90%	0.88
LVEF (%)	Mean	24.4% (+/-6.0)	26.5% (+/-5.1)	0.05
Creatinine Clearance (mL/min)	Mean	61.9 (+/-19.0)	61.8 (+/-21.4)	0.83
Six Minute Walk Test (meters)	Mean	301.6 (+/-104.8)	313.4 (+/-100.1)	0.76
NT-ProBNP (ng/L)	Mean	2132 (+/-2021)	1755 (+/-1842)	0.29

Patient Disposition



Primary Efficacy Endpoint

Efficacy Results Across Pre-specified Primary and Sensitivity Analyses of the Primary Efficacy Endpoint

Events/100 Patient Years	Placebo	Ixymyelocel-T
Treated patients (n=114)	121.73	72.16
Per Protocol (n=109)	109.97	69.76
Sensitivity analysis [a] (n=109)	112.17	69.76

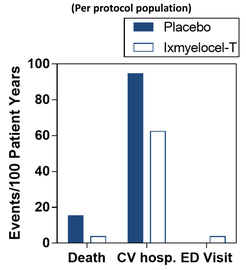
[a] sensitivity analysis includes injection-related events which were excluded from primary efficacy endpoint analysis

Patient Population	P value[a]	Rate Ratio [95% CI]
Treated patients	P=0.0107	0.59 [0.40-0.89]
Per Protocol	P=0.0344	0.63 [0.42-0.97]
Sensitivity Analysis:	P=0.0267	0.62 [0.41-0.95]

[a] Wald chi-square

Treatment with ixmyelocel-T resulted in a 37% reduction in the primary endpoint of all-cause mortality, cardiac hospitalizations, and outpatient treatment of acute decompensated HF at 1 year. Results of pre-specified sensitivity analyses were consistent with the primary endpoint results.

Events*/100 Patient Years for Each Component of the Primary Efficacy Endpoint
(Per protocol population)



*Events occurring after ventricular assist device (VAD) or heart transplant are excluded from efficacy analyses. Two ixmyelocel-T patients received VADs and subsequently died.

Analysis of AICD Interrogations

A pre-specified secondary endpoint included intermittent assessment of AICD interrogation for events defined as ventricular arrhythmia lasting > 30 sec, ventricular tachycardia resulting in shock, and any ventricular arrhythmia resulting in anti-tachycardia pacing. 58/58 ixmyelocel-T patients and 50/51 placebo patients had AICD interrogation during the 12 month follow-up. A Poisson regression of the events per 100 patient years was performed (Wald Chi-Square). Note that the p-values for secondary endpoints such as AICD firing are considered descriptive.

Ventricular Arrhythmias

Events detected by AICD Interrogations

	Placebo (N=50/51)*	Ixmyelocel-T (N=58/58)
Events/100 patient years [a]	310.99	236.42
Rate Ratio [95% CI]		0.76 [0.58, 1.00]
P-Value (unadjusted for multiple comparisons)		0.0502

*One placebo patient had no AICD data collected after treatment and is excluded from analysis.

[a] Patient years reflects the period of AICD interrogation which, for a given patient, may be less than the duration patients were followed for the primary endpoint due to intervals during follow-up where ACID monitoring was not performed.

Patients who received ixmyelocel-T had a 24% reduction in ventricular arrhythmia episodes compared with the placebo group.

Summary of Treatment-Emergent Serious Adverse Events in >2 Patients in Either Treatment Group

MedDRA System Organ Class SAE Preferred Term	Placebo N=55	Ixmyelocel-T N=59
Patients with any SAE, n (%)	**41 (74.5)**	**31 (52.5)**
Cardiac disorders	32 (58.2)	23 (39.0)
Ventricular tachycardia	8 (14.5)	9 (15.3)
Cardiac failure congestive	6 (10.9)	7 (11.9)
Cardiac failure	**7 (12.7)**	**4 (6.8)**
Ventricular fibrillation	**8 (14.5)**	**0 (0.0)**
Chest pain	**5 (9.1)**	**2 (3.4)**
Cardiac failure acute	2 (3.6)	3 (5.1)
Cardiogenic shock	2 (3.6)	3 (5.1)
Vascular disorders	7 (12.7)	5 (8.5)
Hypotension	**4 (7.3)**	**1 (1.7)**
Infections & infestations	7 (12.7)	3 (5.1)
Urinary tract infection	**3 (5.5)**	**0 (0.0)**
Renal & urinary disorders	3 (5.5)	2 (3.4)
Renal failure acute	3 (5.5)	1 (1.7)

SAE=serious adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients treated. Treatment-emergent SAE=SAE that began during or after investigational product injection.

- Serious adverse events occurred in a greater percentage of placebo patients (74.5%) compared with Ixmyelocel-T patients (52.5%).
- There were no SAEs reported more frequently (ie, with a difference of ≥5% between treatment groups) by patients in the ixmyelocel-T group relative to patients in the placebo group.
- SAEs reported more frequently (≥5% difference) by patients in the placebo group relative to patients in the ixmyelocel-T group included **cardiac failure, ventricular fibrillation, chest pain, hypotension,** and **urinary tract infection**.

Ixmyelocel-T patients had fewer ventricular fibrillation events during the 12 month follow-up.

Conclusions

These data suggest that reduction in ventricular arrhythmias may play a role in the clinical benefit observed with ixmyelocel-T multicellular therapy.

Disclosures

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