Five-Year Outcomes of Halt-MS: High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Severe Relapsing-Remitting Multiple Sclerosis

James Bowen, MD
Swedish Neuroscience Institute, Seattle

For the HALT-MS Investigators

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HALT MS: Study Overview

Hypothesis: Intensive immunosuppressive therapy supported by autologous hematopoietic cell infusion will arrest disease activity in individuals with poor-risk MS.

Study design:

Prospective
Open-label
Single-arm
Multicenter
Phase II clinical trial.

Primary Objective: To determine the 5-year durability of disease stabilization in MS subjects after HDIT and autologous HCT.

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Previous Publication

High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Stem Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS): a 3 Year Interim Report

JAMA Neurology 72 (2):159-169, February, 2015

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Primary Endpoint

Event-free survival during the 5 years after high-dose therapy.

Composite endpoint for event-free survival includes one or more of the following:

1. Relapse
   - New neurological S/S persisting > 48 hrs
2. MRI abnormalities (≥12 months post-tx)
   - ≥ 2 or more independent MS lesions
3. Progression in disability (≥ 6 months post-tx)
   - ≥ 1.0 EDSS confirmed > 3 months later
4. Mortality

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Eligibility

1. Age: 18- 60 years, inclusive.
2. Diagnosis of MS using McDonald Criteria.
3. MS duration < 15 yrs from diagnosis.
4. RRMS with cumulative disability or PRMS.
5. EDSS 3.0 – 5.5
6. T2 abnormalities on MRI consistent with MS.
7. ≥2 relapses within 18 months **on therapy**
   with sustained EDSS increase > 0.5 (=0.5 if EDSS 4-5.5)
   or
   1 relapse on therapy with EDSS increase > 1.0 and
   ≥3 gadolinium-enhancing or new T2 lesions on brain or spinal cord MRI (different location, 3-18 months after clinical attack)
8. Approval by MS Review Panel.

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Patient Characteristics (n=25)

Age at Mobilization (years), median (range)	37 (26 – 52)
Gender (F/M)	17/8
Baseline EDSS, median (range)	4.5 (3.0 – 5.5)
Disease Duration (years), median (range)	4.9 (0.6 – 12.0)
Prior therapy (n):	
Interferon Beta-1A	22
Interferon Beta-1B	1
Glatiramer acetate	18
Mitoxantrone	8
Natalizumab	6
Other	11

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PBSC Mobilization with G-CSF

Day	0	1	2	3	4	5	
Prednisone* (1 mg/kg/day) x10 days	X	X	X	X	X	X	→
G-CSF (16 μg/kg/day)		X	X	X	X	X	→
Leukapheresis					X	X	→

CD34 selection with Baxter Isolex 300i system:

≥ 2.0 x 10^6 CD34 positive cells/kg required for transplant.

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Collection of Hematopoietic Stem Cells and Engraftment after Transplant

Number of collections:

Collection #	Patient (n)
1	5
2	15
3	5

One patient failed mobilization with G-CSF/prednisone and required mobilization with cyclophosphamide.

All patients collected ≥2.0 x10^6 CD34-selected cells/kg (n=25).

No delayed engraftment events were observed.

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High-Dose Immunosuppressive Therapy Regimen (BEAM + ATG)

(**B**CNU, **E**toposide, **A**ra C, **M**elphalan)

HDIT

Day -6 BCNU 300 mg/m^2 IV
-5 VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
-4 VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
-3 VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
-2 VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
rATG 2.5 mg/kg IV
-1 Melphalan 140 mg/m^2 IV; rATG 2.5 mg/kg IV
0 CD34+ HSC infusion

Post-transplant

G-CSF from Day +5 until ANC >500/uL.

Prednisone 0.5 mg/kg/day from Day +7-21 then taper over 2 weeks.

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Adverse Events

- AE grade 2 and above were recorded EXCEPT during the peri-transplant period (from the start of conditioning until Day 60 after transplant) when only grade 3 and above were recorded.

- Total Adverse Events: 399 among 25 patients
- Total Serious Adverse Events: 66 among 16 patients

	AE Start Time	
Severity*	Prior to Year 3	Year 3 and Beyond
Grade 1 or 2	145	18
Grade 3	124	14
Grade 4	94	0
Grade 5	1	2

*one ungraded pregnancy AE is not included in table

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Non-hematopoietic and Non-GI Adverse Events after High-Dose Immunosuppressive Therapy (Gr 4 and 5 NCI CTC)

Grade	Event	Patients (n)	Events (n)
4	Manic Depression/Suicide Attempt/Respiratory Failure	1	3
	Suicide attempt	1	1
	Respiratory arrest/failure	1	1
	Hypokalemia	1	1
	Pulmonary Embolism (HIT)	1	1
	Hyperuricemia	1	1
	Increased ALT	1	1
5	MS Progression at >2 years	1	1
	Anoxic encephalopathy at >3 years	1	1
	Cardio-respiratory arrest at >4 years	1	1

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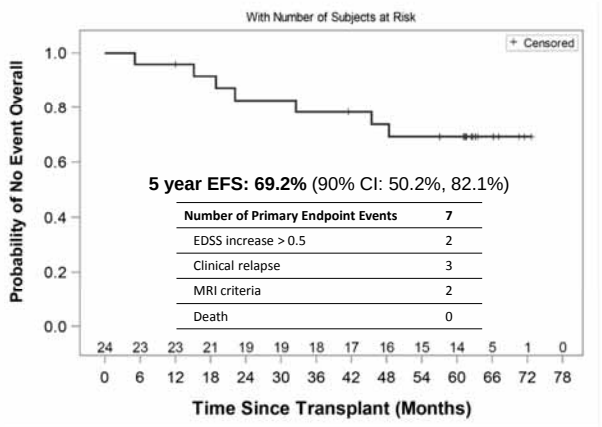
Primary Endpoint: Event-Free Survival



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Primary and Subsequent Endpoints

Primary endpoint events AND subsequent endpoints are captured in the clinical database

Subject ID	Endpoint Event Date/Month	Endpoint Met
203102	**12NOV2010/45.5**	**MRI criteria**
2031034	**23FEB2009/18.9**	**EDSS increase > 0.5**
	21MAR2010/31.8	Death
2031068	**17JAN2012/48.4**	**MRI criteria**
2031111	**06OCT2010/22.2**	**Clinical relapse**
2031144	**23FEB2010/5.1**	**Clinical relapse**
	16SEP2010/11.9	MRI criteria
	03AUG2013/46.5	Death
2031158	**15NOV2012/32.6**	**Clinical relapse**
2109025	**03MAY2011/15.2**	**EDSS increase > 0.5**
	26JUL2014/54.1	Death

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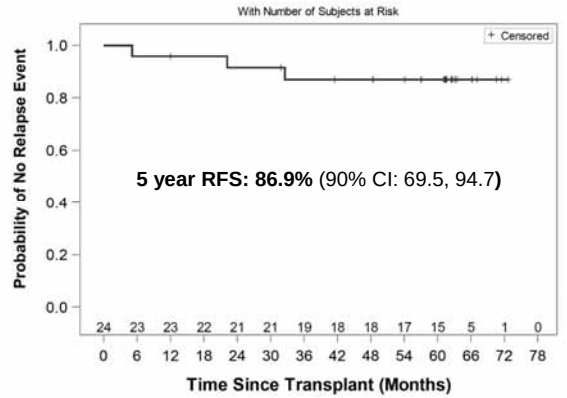
Relapse-Free Survival



5 year RFS: 86.9% (90% CI: 69.5, 94.7**)**

Note: Upon meeting primary endpoint, a participant is not censored from further events in the remaining components.

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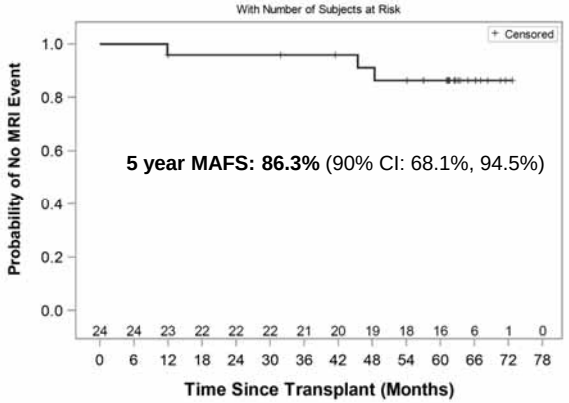
MRI Activity-Free Survival



5 year MAFS: 86.3% (90% CI: 68.1%, 94.5%)

Note: Upon meeting primary endpoint, a participant is not censored from further events in the remaining components. The MRI event that occurred at 11.9 months was not a primary endpoint event, but rather an event that occurred subsequently after the subject met primary endpoint via clinical relapse at 5.1 months

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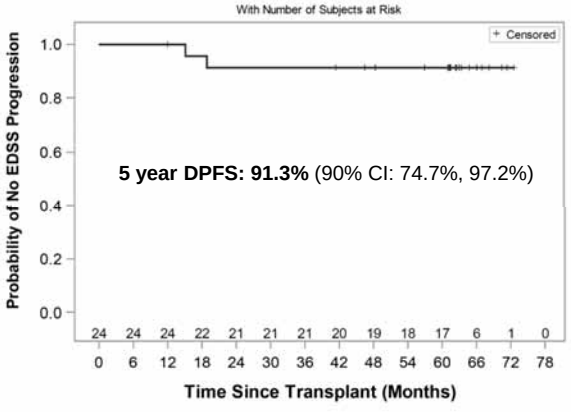
EDSS Progression-Free Survival



5 year DPFS: 91.3% (90% CI: 74.7%, 97.2%)

Note: Upon meeting primary endpoint, a participant is not censored from further events in the remaining components.

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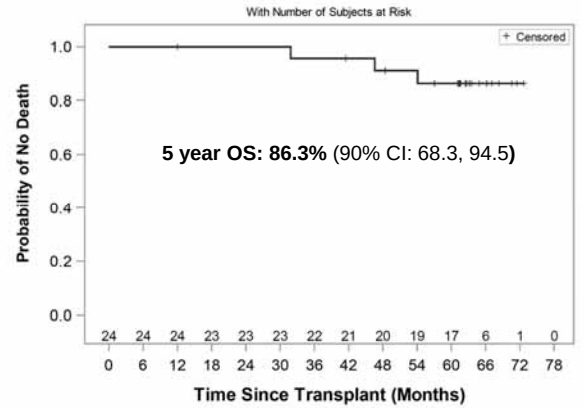
Overall Survival



5 year OS: 86.3% (90% CI: 68.3, 94.5**)**

Note: Upon meeting the primary endpoint, a participant is not censored from further events in the remaining components. In each of the 3 deaths, the subject previously met primary endpoint via another criterion.

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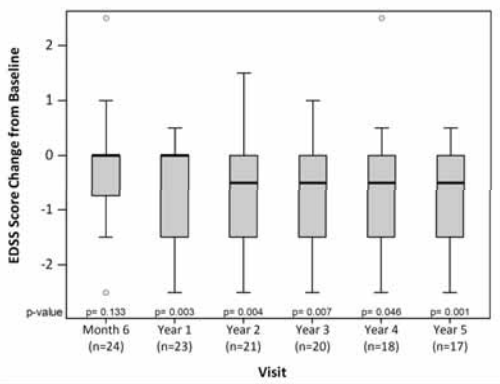
Change in EDSS



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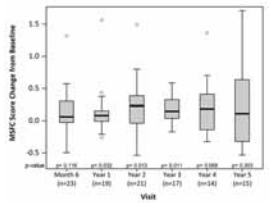
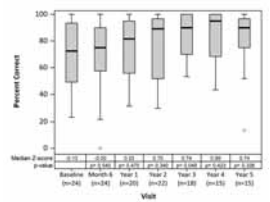
Change in MSFC Total Score and Summary of Components

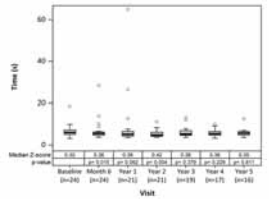
MSFC Score



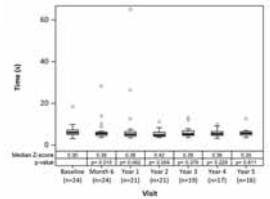
PASAT, % correct



9-hole Peg Test (avg. of both hands)



Time 25-foot walk



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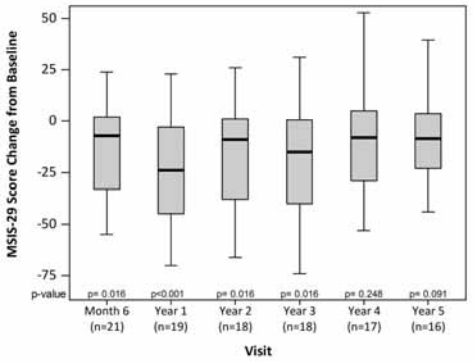
Change in MS Impact Scale (MSIS-29)



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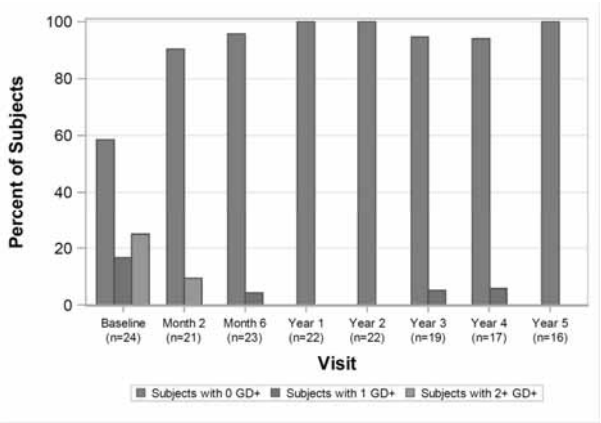
Changes in Gadolinium Enhancing Lesions



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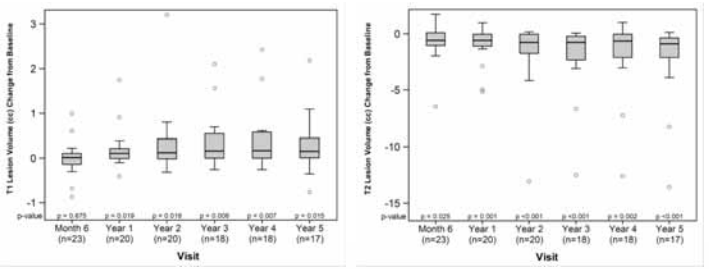
Change from Baseline in T1 and T2 Lesion Volume



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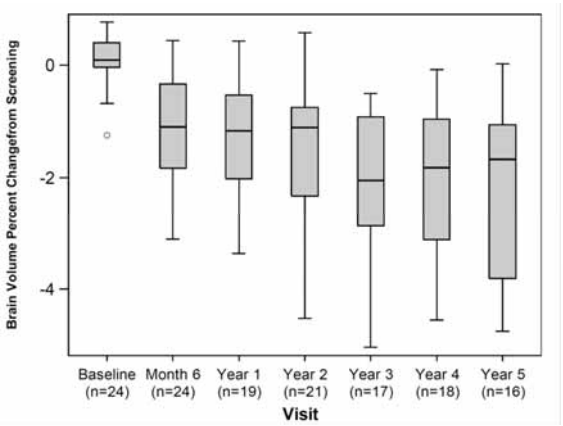
Percent Change in Brain Volume from Screening



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Conclusions

1. High-dose immunosuppressive therapy was well-tolerated with few serious early complications.
2. High-dose immunosuppressive therapy was highly effective for inducing sustained remissions of highly active RRMS through Year 5. No disease-modifying therapy was administered after transplant unless the subject experienced relapse or increase in EDSS.
3. EDSS was improved at Year 1 and sustained through Year 5.
4. Brain volume stabilized at Year 3 through Year 5.

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Investigators (HALT MS; ITN033AI)

Neurology Investigators
- Jim Bowen - Swedish Neurosci
- George Kraft - UW
- Annette Wundes - UW
- George Hutton - Baylor
- Michael Racke – OSU

Consultant Neurologists
- Paolo Muraro - Imperial College
- Harry Openshaw - COH
- Olaf Stuve - UTSW
- Doug Arnold - McGill

Transplant Physicians
- Steve Devine – OSU
- Uday Popat - MD Anderson
- George Georges - UW/FHCRC

Study Monitors
- Linda Griffith - NIAID/NIH
- Peter Sayre – ITN

Statisticians
- Kaitlyn McConville – Rho
- James Rochon - Rho

Immune Tolerance Network

NIAID
National Institute of Allergy & Infectious Diseases

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