High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS

ABSTRACT

Objective: To evaluate the safety, efficacy, and durability of multiple sclerosis (MS) disease stabilization after high-dose immunosuppressive therapy (HDIT) and autologous hematopoietic cell transplantation (HCT).

Methods: High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) is a phase II clinical trial of HDIT/HCT for patients with relapsing-remitting (RR) MS who experienced relapses with disability progression (Expanded Disability Status Scale [EDSS] 3.0–5.5) while on MS disease-modifying therapy. The primary endpoint was event-free survival (EFS), defined as survival without death or disease activity from any one of: disability progression, relapse, or new lesions on MRI. Participants were evaluated through 5 years posttransplant. Toxicities were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (AE).

Results: Twenty-five participants were evaluated for transplant and 24 participants underwent HDIT/HCT. Median follow-up was 62 months (range 12–72). EFS was 69.2% (90% confidence interval [CI] 50.2–82.1). Progression-free survival, clinical relapse-free survival, and MRI activity-free survival were 91.3% (90% CI 74.7%–97.2%), 86.9% (90% CI 69.5%–94.7%), and 86.3% (90% CI 68.1%–94.5%), respectively. AE due to HDIT/HCT were consistent with expected toxicities and there were no significant late neurologic adverse effects noted. Improvements were noted in neurologic disability with a median change in EDSS of –0.5 (interquartile range –1.5 to 0.0; p = 0.001) among participants who survived and completed the study.

Conclusion: HDIT/HCT without maintenance therapy was effective for inducing long-term sustained remissions of active RRMS at 5 years.

ClinicalTrials.gov identifier: NCT00288626.

Classification of evidence: This study provides Class IV evidence that participants with RRMS experienced sustained remissions with toxicities as expected from HDIT/HCT. Neurology® 2017;88:1-11

GLOSSARY

AE = adverse event; ASTIMS = Autologous Stem Cell Transplantation International MS Trial; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; EFS = event-free survival; FDA = Food and Drug Administration; HALT-MS = High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis; HCT = hematopoietic cell transplantation; HDIT = high-dose immunosuppressive therapy; IgG = immunoglobulin G; IQR = interquartile range; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS = Multiple Sclerosis Impact Scale; MSRP = Multiple Sclerosis Review Panel; NEDA = no evidence of disease activity; OCB = oligoclonal bands; QoL = quality of life; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Multiple sclerosis (MS) is an autoimmune disease resulting in demyelination and loss of CNS neurons. The High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) clinical trial was initiated in participants with relapsing-remitting MS (RRMS); that is, with active CNS inflammation relatively early in the disease course.1 We

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hypothesized that high-dose immunosuppressive therapy (HDIT) and autologous hematopoietic cell transplantation (HCT) would remove disease-causing cells and induce a reset of the immune system, thereby controlling disease.\textsuperscript{2,3} Participants had substantial disability progression (Expanded Disability Status Scale [EDSS] 3.0–5.5) and failure of MS disease-modifying therapy (DMT) to control disease activity. At 3 years after HDIT/HCT, and, importantly, with no posttransplant immunosuppressive therapy administered, event-free survival (EFS) was 78%,\textsuperscript{1} defined as absence of progression, relapse activity, or new MRI lesions. Further, peritransplant adverse events (AE) were consistent with those routinely observed after HDIT/HCT,\textsuperscript{1} and treatment-related mortality was zero.\textsuperscript{1} In this report, outcomes of participants followed at least 5 years are described.

Outcomes at 5 years for participants in the HALT-MS clinical trial compare favorably to results from nontransplant studies that enrolled participants with less severe MS and followed them for only 2–3 years.\textsuperscript{4} HALT-MS is among the first MS treatment clinical trials to use a composite endpoint for EFS that is comparable, but not identical, to no evidence of MS disease activity (NEDA) (including MRI activity, relapse, or progression of disability)\textsuperscript{4,5} as the primary endpoint. Advantages of the composite endpoint include that (1) it is a sensitive indicator of MS disease activity as compared to either relapse activity or progression of disability alone and (2) it facilitates comparison of HDIT/HCT to other MS DMT.\textsuperscript{4} For current Food and Drug Administration (FDA)–approved therapies for MS, including glatiramer acetate or interferon-\(\beta\)-1a (first-line treatments\textsuperscript{6}), or natalizumab or alemtuzumab (second-line treatments\textsuperscript{6}), NEDA levels of 19%, 21%, 37%, and 39%, respectively, were observed with follow-up of 2–3 years after initiation of study treatment.\textsuperscript{5–8} In an observational clinical cohort in which participants received no or multiple different therapies, NEDA was maintained at 1 year in 46%, but at 7 years in only 7% of participants with MS.\textsuperscript{9}

**Patients.** Eligible patients were 18–60 years of age and had MS by McDonald criteria\textsuperscript{10} with (1) RRMS; (2) EDSS\textsuperscript{11} 3.0–5.5 at baseline; (3) lesions on brain MRI consistent with MS; (4) disease duration <15 years; and (5) failure of DMT, defined as \(\geq\)2 clinical relapses over 18 months while on therapy and associated with EDSS increase (by 1.0 for EDSS of 3.0–3.5 or by 0.5 for EDSS of 4.0–5.5 and sustained \(\geq\)4 weeks). Eligibility was determined by a MS Review Panel (MSRP).\textsuperscript{1}

**Standard protocol approvals, registrations, and patient consent.** The clinical study (protocol ITN033AI; BB-IND 12164; type II DMF BB-IND 118211) was approved by institutional review boards at participating sites and participants provided written informed consent. The clinicaltrials.gov registration number is NCT00288626.

**Study design.** This is a prospective, open-label, single-arm, multicenter phase II clinical trial.

**Procedures.** Autologous peripheral blood stem cells were collected, CD34-selected, and stored as described.\textsuperscript{1} High-dose chemotherapy was carmustine (BCNU) 300 mg/m\(^2\) on day –6, etoposide 200 mg/m\(^2\) and cytarabine 200 mg/m\(^2\) daily from day –5 to –2, and melphalan 140 mg/m\(^2\) on day –1 (BEAM).\textsuperscript{1,12} Rabbit antithymocyte globulin (2.5 mg/kg/d) was administered on days –2 and –1. On day 0, CD34+ hematopoietic progenitor cells were thawed and infused. Filgrastim (5 \(\mu\)g/kg/d) was administered from day +5 until recovery of blood counts. Prednisone was administered (0.5 mg/kg/d) from day +7 to +21 and then tapered over 2 weeks to prevent engraftment syndrome. Supportive care was administered as described.\textsuperscript{13}

**Primary endpoint and study evaluations.** The primary endpoint was time until treatment failure or EFS during 5 years post-HCT, defined as the first event of death or disease activity from any one of: (1) disability progression, (2) relapse, or (3) new lesions on MRI. Disability progression was defined as a change in EDSS performed at least 6 months after transplant of \(>0.5\) as compared to EDSS at baseline and confirmed 3 months later.\textsuperscript{1} Relapse was defined as new neurologic symptoms lasting over 48 hours. The MRI endpoint was 2 or more gadolinium-enhancing or new T2-weighted lesions at 1 year or longer after transplant. The Multiple Sclerosis Functional Composite (MSFC) and the Multiple Sclerosis Impact Scale (MSIS-29) were performed before mobilization of stem cells, at +6 months, and then annually to end of study. Participants were contacted by telephone between annual visits at an interval of 3 months and if there were new neurologic symptoms, they were evaluated.

Brain MRI was performed at screening post-MSRP, baseline, +2 months, +6 months, and then annually to +5 years, on scanners with 1.5T field strength. Scans were analyzed centrally (NeuroRx, Montreal, Canada). The brain MRI at +2 months was the post-treatment reference scan for assessment of treatment failure. The pretreatment screening scan was the reference for brain volume changes.

Toxicities were reported by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. AE \(\geq\) grade 2 were recorded from 3 to 5 years of the study.

Oligoclonal bands (OCB) were identified/quantified by 2 independent experienced readers following isoelectric focusing on agarose and in-gel enzyme-enhanced immunostaining using an FDA-approved method (Sebia [Norcross, GA] Isofocusing Gel), following consensus guidelines.\textsuperscript{14} Total immunoglobulin G (IgG) concentrations were measured in CSF and serum specimens to allow normalization of the concentration of IgG applied to each gel lane. Participant paired CSF and serum samples from

**METHODS** Details of the patient population, procedures, evaluations, and study design have been reported.\textsuperscript{1}
baselines, 2 years, and 4 years posttransplant were assayed on the same gel for accurate comparison of bands. Bands visualized in CSF but not in paired serum specimens were denoted as CSF-specific. Disappearance/resolution of CSF-specific bands and appearance of novel CSF-specific bands in the +2 years and +4 years specimens as compared to the baseline sample of each participant were recorded. Analyses were performed in a CLIA-certified laboratory (Department of Laboratory Medicine, University of Washington, Seattle).

Statistics. EFS was calculated using the Kaplan-Meier method to assess the composite primary endpoint. Similar analyses were conducted for the individual components of disability progression, clinical relapse, new MRI lesions, and death to produce progression-free, relapse-free, MRI activity-free, and overall survival estimates. Follow-up for any component was not censored by earlier events so that each has an interpretation independent of the other components. Standard errors were derived using the Greenwood formula and used to generate 90% confidence intervals (CIs).

Secondary outcomes included change in T1 and T2 lesion volumes, total brain volume, EDSS, MSFC, and MSIS. Each component of the MSFC was transformed into a Z score using the National MS Society Task Force Database reference population. Significant change from baseline was tested using the Wilcoxon signed-rank test. The screening measurement was used as the reference for percent change in brain volume, while the baseline visit was used for all other endpoints. A limitation of this study is that for secondary outcomes no corrections have been made for multiple comparisons, as this pilot study was hypothesis-generating and not a formal test of specific hypotheses.

All analyses were performed using SAS version 9.3 (Cary, NC) or higher. Datasets for the analyses are available through TrialShare, a public website managed by the Immune Tolerance Network (https://www.itntrialshare.org/HALTMS_5yr.url).

Primary research question. To assess the 5-year durability of disease stabilization in patients with MS after HDIT and autologous HCT.

Classification of evidence. This study provides Class IV evidence that participants with RRMS experienced sustained remissions with toxicities as expected from HDIT/HCT.

RESULTS Patient characteristics. Twenty-five patients were consented and 24 patients underwent HDIT/HCT (figure 1, and figure e-1 and table e-1 at Neurology.org). The 25 entering participants had median age 37 years (interquartile range [IQR] 31–42), with 17 (68%) women. Disease duration was 4.9 years (median; IQR 2.5–7.3); baseline EDSS was 4.5 (median; IQR, 4.0–5.0). Participants had previously failed 3 (median; IQR 2–4) nontransplant MS medications.

Adverse events. AEs to 3 years after transplant were described, and were consistent with toxic effects associated with HDIT/HCT, including predominantly cytopenias and infections; no acute treatment-related neurologic AE were observed. Beyond 3 years post-HCT, 15 grade 3 AEs occurred (table 1); no grade 4 AEs were observed.

Two participants had disease progression and died (grade 5 AE) at 2.5 years and 3.5 years after transplant and were reported. A third participant also had disease progression at 15 months and died at 4.5 years post-HCT. No information was available on the events leading up to death. The final cause of death was cardiopulmonary arrest. No death was attributed to transplant.

Evaluation of disease. The estimated EFS probability was 73.8% (90% CI 55.0%–85.7%) at 4 years and 69.2% (90% CI 50.2%–82.1%) at 5 years. Of 24 participants transplanted, 7 did not maintain EFS by close of follow-up (figure 2, A–B and table e-2) by an increase in EDSS >0.5 (n = 2), clinical relapse (n = 3), or development of new MRI lesions (n = 2). The 5-year progression-free survival was 91.3% (90% CI 74.7%–97.2%), relapse-free survival was 86.9% (90% CI 69.5%–94.7%), MRI activity-free survival was 86.3% (90% CI 68.1%–94.5%), and overall survival was 86.3% (90% CI 68.3%–94.5%) (figure 2, C–F, and table e-2).

Three of 24 participants transplanted did not maintain EFS due to clinical relapse, at 5.1, 22.2, and 32.6 months. However, for all participants, including those failing to maintain EFS, relapse activity was reduced posttransplant as compared to pre-treatment (figure 1).

The EDSS score, for participants who survived and completed the study, improved after transplant with a median change from baseline of −0.50 (IQR −1.5 to 0.0) at 5 years (p = 0.001; figure 3A and table e-3). Specifically, as compared to baseline pre-transplant, 15 participants had improvement (≥0.5 decrease) in EDSS, 5 remained stable (no change), and 4 progressed (≥0.5 increase) at the time of their last EDSS assessment, with 2 failing to maintain EFS due to progression at 15.2 and 18.9 months. The MSFC improved from baseline (figure 3, B–E, and table e-3) by 1 year and this persisted through 3 years after transplant, but by year 5 significant improvement was not sustained (p = 0.303). MSIS-29 quality of life (QoL) was improved at 3 years; however, only a trend towards improvement was noted at the end of the study (median −8.50; IQR −23 to 3.5; p = 0.091) (figure 3F and table e-3).

MRI assessments. Two participants failed to maintain EFS at 45.6 and 48.4 months posttransplant due to development of new brain gadolinium-enhancing lesions or T2 lesions (figure 4, A and B). For all participants, T2 lesion volume decreased during follow-up starting at 6 months; at 5 years, there was still a decrease (p < 0.001) (figure 4C). T1 lesion volume demonstrated a median increase from baseline and at year 5 remained different from zero (p = 0.015) (figure 4D). Brain volume was decreased at 6 months as compared to baseline, but subsequently appeared to stabilize (figure 4E). Thus, while brain
volume at the end of the study was decreased compared to baseline, there was no change in brain volume from year 3 to the end of the study.

**OCB evaluation.** To investigate the effect of transplant on presence of OCB in the CSF, participant samples were analyzed at baseline and at 2 and 4 years post-HCT. There was persistence but a reduction in OCB number in the CSF at 2 years (figure e-2), with a reduction of CSF IgG levels after transplant.

**DISCUSSION** In this 5-year analysis of HDIT/HCT without posttransplant maintenance therapy for participants with highly active RRMS in the HALT-MS study, 69.2% of participants remained event-free without evidence of relapse, disability progression, or new MRI lesions. These outcomes are highly promising, as compared to non-HCT treatments, and consistent with other contemporary investigations of autologous HCT for similarly afflicted individuals.

Highly active RRMS is the target population for contemporary investigations of HDIT/HCT for MS. Uniquely, among participants involved in earlier exploratory studies, those with RRMS demonstrated favorable responses, including some who experienced improved...
EDSS, while those with advanced primary progressive MS or secondary progressive MS (SPMS) continued to experience disability progression, possibly due to an irreversible neurodegenerative process with progression resulting from earlier immunologic injury.12,22–25 Outcomes of HDIT with autologous HCT are similar across contemporary clinical trials including HALT-MS with regard to inducing sustained remissions and stability of neurologic function in participants with RRMS.4 For other contemporary investigations in which disease activity-free survival was determined, with events consisting of death or disease activity from any one of EDSS progression, relapse activity, or new MRI lesions, 68% of participants at 5 years in the Swedish experience,16 68% of participants at 4 years in the Canadian study,18 and 69.6% of participants at 3 years in the Canadian study18 remained event-free. Further, in the Canadian study, none of 24 participants experienced relapses or new MRI activity and only 7 of 24 participants (29%) experienced further disability progression at a median follow-up of 6.7 years.18 For 25 participants with RRMS reported from Italy, relapse-free survival was 70% and progression-free survival was 71% at 5 years.19

As detailed in our interim report, AEs observed in the HALT-MS study were consistent with those routinely observed after HDIT/HCT.1 AEs recorded at 4 and 5 years were not related to the transplant and, in general, were not considered severe. A third death occurred at 4.5 years posttransplant due to cardiorespiratory arrest; the 2 deaths reported previously1 were also late posttransplant at 2.5 and 3.5 years. These participants had all experienced worsening of MS, and no death was related to the study treatment.

In other contemporary studies of HDIT/HCT for RRMS, mortality has been 0%–4%.16–19,21,26 Regarding treatment-related mortality, 1 death among 24 participants in the Canadian study,18 and 2 deaths among 74 participants in the Italian experience were attributed to transplant-related complications (a third death in that series also occurred within 3 months of transplant but was attributed to other causes).19 One death occurred among 151 participants at Northwestern University, at 30 months posttransplant, from hypertensive cardiovascular disease.17 Overall survival in these studies has otherwise been 100% for the Autologous Stem Cell Transplantation International MS Trial (ASTIMS) randomized study (9 participants received transplant)21 and for the Swedish prospective observational study of 48 participants.16 These data are consistent with the recent EBMT registry report of 100-day, treatment-related mortality of 2% (for 345 MS cases), which was observed to be lower in experienced centers.26 In comparison, in a nontransplant group of patients with MS with EDSS of 3.5–5.5, MS-related mortality was 19% at 20 years of follow-up.27

Table 1 Adverse events (AEs) by time of occurrence

<table>
<thead>
<tr>
<th>Time of AE occurrenceb</th>
<th>Enrolled participants (n = 25)</th>
<th>Grade 3c</th>
<th>Participants, %d,e</th>
<th>Events, n</th>
<th>Grade 4c</th>
<th>Participants, %d,e</th>
<th>Events, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td></td>
<td></td>
<td>23 (92.0)</td>
<td>138</td>
<td>25 (100)</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Prior to start of mobilization</td>
<td>1 (4.0)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobilization until start of conditioningf</td>
<td>10 (40.0)</td>
<td>20</td>
<td>5 (20.0)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of conditioning to day 29</td>
<td>20 (80.0)</td>
<td>53</td>
<td>24 (96.0)</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 30-99</td>
<td>8 (32.0)</td>
<td>13</td>
<td>1 (4.0)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 100-364</td>
<td>6 (24.0)</td>
<td>12</td>
<td>2 (8.0)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1 to &lt; year 2</td>
<td>4 (16.0)</td>
<td>15</td>
<td>1 (4.0)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2 to &lt; year 3</td>
<td>6 (24.0)</td>
<td>9</td>
<td>1 (4.0)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3 to &lt; year 4</td>
<td>7 (28.0)</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥Year 4</td>
<td>3 (12.0)</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

a AEs from prior to start of mobilization through completion of year 3 post-hematopoietic cell transplantation (HCT) are reported in greater detail in the interim report for this study (Nash et al.,1 table 2).
b Three deaths occurred (grade 5 AEs) at 2.6, 3.9, and 4.5 years after HCT. All participants had previously experienced worsening of multiple sclerosis and met primary endpoint. No death was attributed to transplant.
c Thirty-eight (28%) of the grade 3 AEs and 85 (90%) of the grade 4 AEs were hematopoietic or gastrointestinal.
d Participants who experienced one or more adverse events are counted only once.
e Percentages for the number of participants with AEs are based on the number of participants in the safety population.
f One participant who was mobilized, but not subsequently transplanted, is included. This participant experienced 3 AEs, which all began between 1.0 and 1.2 days after the start of mobilization. These events are included in the “mobilization until start of conditioning” time category. The events include a grade 3 arteriovenous malformation, a grade 3 lymphopenia, and a grade 4 pulmonary embolism.
In another report of non-transplant patients with MS with an EDSS of 3.0–5.5, mortality was 22% at 15 years. Although there were no treatment-related deaths in the HALT-MS study, there is a significant risk associated with transplant and patients require counseling regarding this.
Figure 3  Clinical outcomes

(A) Expanded Disability Status Scale (EDSS). (B) Multiple Sclerosis Functional Composite (MSFC). (C) MSFC component: 3-second Paced Auditory Serial Addition test (PASAT-3). (D) MSFC component: 9-Hole Peg Test. Average of trials from the dominant and nondominant hands. (E) MSFC component: Timed 25-Foot Walk Test. (F) Quality of life: 29-item Multiple Sclerosis Impact Scale (MSIS-29). The *p* values from a Wilcoxon signed-rank test are presented at each postbaseline visit along the x-axis assessing the change from baseline. The *p* value in the MSFC components in panels C through E assesses a change in the component Z score from baseline. The median component Z scores can be found in table e-3.
The primary goal of HDIT/HCT in the HALT-MS clinical trial was to suppress active disease and prevent further disability. In addition, we note that participants who survived and completed the study experienced a median improvement in EDSS by a score of 0.5. In the contemporary Italian experience,

(A) New gadolinium-enhancing (GD+) lesions occurring after transplant. The GD+ lesions as seen at years 3 and 4 are 2 different GD+ lesions observed in the same participant, and thus this individual met primary endpoint. (B) New T2 lesions since previous visit. The new T2 lesions seen at year 4 are in one individual, who met primary endpoint. (C) T2 lesion volume (mL) change from baseline. There was a decrease in T2 lesion volume at year 5 ($p < 0.001$). (D) T1 lesion volume (mL) change from baseline. There was an increase in T1 lesion volume at year 5 ($p < 0.015$). (E) Percentage of change in brain volume from screening. At year 5, brain volume was significantly decreased compared to baseline ($p < 0.001$) however, there was stabilization in brain volume from year 3 to 5 ($p = 0.311$) after transplant.
8 of 25 (31%) participants with RRMS experienced improvement of >1 EDSS point at 6–12 months after HDIT/HCT, compared with 1 of 36 with SPMS.\textsuperscript{19} At Northwestern University, it was noted that 17 of 21 (81%) participants with RRMS had an EDSS improvement of at least 1 point at a mean of 37 months post-HCT.\textsuperscript{20} In a larger study that included RRMS and SPMS from the same group, the baseline EDSS was 4.0, which improved to 2.5 at 4 years after HDIT/HCT.\textsuperscript{17} Therefore, patients with RRMS and relatively low EDSS scores may have more potential for recovery of neurologic function as compared to those with greater disability.

A markedly reduced risk of recurrent or new lesions on MRI has been observed for contemporary studies of HDIT/HCT for RRMS. This is important because appearance of new MRI lesions has been demonstrated to be correlated with relapse activity\textsuperscript{29} and with progression.\textsuperscript{28} For HALT-MS, a decrease in T2 lesion volume was observed through 5 years, and only 2 participants failed to maintain EFS by developing new lesions late after transplant. In the ASTIMS randomized study, HDIT/HCT significantly reduced MRI activity as compared to treatment with mitoxantrone.\textsuperscript{21} In the Italian experience, only 2 of 24 participants with MRI assessments at 1–2 years post-HCT had new gadolinium-enhancing lesions.\textsuperscript{19} At Northwestern University, there was a significant reduction in new gadolinium-enhancing lesions and T2 lesion volume after transplant.\textsuperscript{17} Of note, participants with active inflammation on MRI at baseline had a lower risk of progression after HDIT/HCT, as compared to those without inflammation.\textsuperscript{16,19,31}

In the HALT-MS study, participants had stabilization of brain volume at 3 years through study conclusion at 5 years, consistent with attenuation of brain tissue loss following resolution of brain inflammation. A significant decrease in brain volume early after HDIT/HCT was noted in earlier studies, raising concern for brain atrophy, possibly due to high-dose chemotherapy.\textsuperscript{32,33} However, in 3 other contemporary studies, at time points beyond 2 years the rate of brain volume loss was observed to decrease, approaching normal for age.\textsuperscript{18,34,35}

The MSIS was used in the HALT-MS study to measure function and QoL, and showed improvement during the first 3 years after transplant, with a trend towards improvement that did not maintain significance at 5 years. At Northwestern University, using the Short Form–36, a similar analysis demonstrated improvement at 4 years but not at 5 years,\textsuperscript{17} with the smaller number of participants available at 5 years possibly resulting in a loss of significance.

Investigation of the immunologic status of participants in the HALT-MS study with sustained remission at 5 years post-HCT vs those with disease activity may contribute to understanding mechanisms of disease in MS. We have shown that dominant CD4+ T-cell clones present pre-HCT were undetectable at 1 year post-HCT, whereas dominant CD8+ clones were not removed.\textsuperscript{3} Furthermore, participants who failed to respond to treatment had less diversity in their T-cell repertoire.\textsuperscript{3} Additional studies are currently underway.

Accumulating evidence supports preemptive treatment to prevent MS disease activity, to achieve best long-term outcomes.\textsuperscript{9,36,37} For patients failing first-line treatments, significantly more potent options are becoming available.\textsuperscript{6,37} We suggest that HDIT/HCT may be a reasonable consideration for such patients. Prospective clinical trials comparing HDIT/HCT to other approaches are needed.\textsuperscript{38} HDIT/HCT may represent a potential therapeutic option for patients with RRMS who fail conventional immunotherapy.

**AUTHOR CONTRIBUTIONS**

Richard A. Nash: study concept or design, drafting of manuscript, study supervision or coordination, acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Michael K. Racke: acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Steven M. Devine: acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Kaitlyn C. Steinmiller (Rho, Inc.): statistical analysis, drafting of manuscript, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Linda M. Griffith: study concept or design, drafting of manuscript, study supervision or coordination, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Paolo A. Muraro: study concept or design, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Harry Openshaw: study concept or design, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Peter H. Sayre (ITN): study concept or design, study supervision or coordination, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Olaf Stuve: analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Douglas L. Arnold (NeuroRx): study concept or design, study supervision or coordination, acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Mark H. Werner: acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. George E. Georges: acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. George J. Hutton: acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Richard A. Nash: study concept or design, drafting of manuscript, study supervision or coordination, acquisition of data, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Dr. Richard A. Nash and Kaitlyn Steinmiller had full access to all study data and take responsibility for the integrity of the data and accuracy of the data analysis.

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