Reduction of Disease Activity and Disability With High-Dose Cyclophosphamide in Patients With Aggressive Multiple Sclerosis

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Objective: To explore the safety and effectiveness of high-dose cyclophosphamide (HiCy) without bone marrow transplantation in patients with aggressive multiple sclerosis (MS).

Design: A 2-year open-label trial of patients with aggressive relapsing-remitting multiple sclerosis (RRMS) given an immunoablative regimen of HiCy (50 mg/kg/d for 4 consecutive days) with no subsequent immunomodulatory therapy unless disease activity reappeared that required rescue therapy.

Setting: The Johns Hopkins University Multiple Sclerosis Center, Baltimore, Maryland.

Patients: A total of 21 patients with RRMS were screened for eligibility and 9 patients were enrolled in the trial. Patients were required to have 2 or more gadolinium-enhancing lesions on each of 2 pretreatment magnetic resonance imaging scans, at least 1 clinical exacerbation in the 12 months prior to HiCy treatment, or a sustained increase of 1.0 point or higher on the Expanded Disability Status Scale (EDSS) in the preceding year.

Intervention: Patients received 50 mg/kg/d of cyclophosphamide intravenously for 4 consecutive days, followed by 5 µg/kg/d of granulocyte colony-stimulating factor 6 days after completion of HiCy treatment, until the absolute neutrophil count exceeded 1.0 × 10^9 cells/L for 2 consecutive days.

Main Outcome Measures: The primary outcome of the study was the safety and tolerability of HiCy in patients with RRMS. Secondary outcome measures included a change in gadolinium-enhancing lesions on magnetic resonance images and a change in disability measures (EDSS and Multiple Sclerosis Functional Composite).

Results: Nine patients were treated and followed up for a mean period of 23 months. Eight patients had failed conventional therapy and 1 was treatment naive. The median age at time of entry was 29 years (range, 20-47 years). All patients developed transient total or near-total pancytopenia as expected, followed by hematopoietic recovery in 10 to 17 days, stimulated by granulocyte colony-stimulating factor. There were no deaths or unexpected serious adverse events. There was a statistically significant reduction in disability (EDSS) at follow-up (mean [SD] decrease, 2.11 [1.97]; 39.4%; P = .02). The mean (SD) number of gadolinium-enhancing lesions on the 2 pretreatment scans were 6.5 (2.1) and 1.2 (2.3) at follow-up (81.4% reduction; P = .01). Two patients required rescue treatment with other immunomodulatory therapies during the study owing to MS exacerbations.

Conclusion: Treatment with HiCy was safe and well tolerated in our patients with MS. Patients experienced a pronounced reduction in disease activity and disability after HiCy treatment. This immunoablative regimen of cyclophosphamide for patients with aggressive MS is worthy of further study and may be an alternative to bone marrow transplantation.

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Because of this clinical and immunopathologic heterogeneity, immunomodulatory strategies to treat MS have been suboptimal. Current Food and Drug Administration–approved immunomodulatory therapies for MS do not abolish inflammation or disease progression, and the vast majority of patients continue to accrue progressive disability despite these therapies.

Cyclophosphamide (Cy) and its active metabolites diffuse into cells and are converted into the alkylating compound phosphoramid mustard through simple intracellular decomposition. Cyclophosphamide is a nonspecific immunosuppressant that affects both T- and B-cell function, and in MS may suppress interleukin (IL)–12 and T-helper type 1 (Th1)–type responses and enhance Th2/Th3 responses. These changes are transient when Cy is given by standard pulse doses, and the immune system returns to baseline within a few months to a year after cessation.

Cyclophosphamide has been used extensively in treating MS, with mixed results. In several studies, pulse Cy alone or in combination with corticotropin (adrenocorticotropic hormone) or interferon resulted in stabilization or improvement in many patients, though toxicity was a major limitation of these regimens. In others, standard induction regimens of Cy with or without pulse boosters did not halt disease progression in patients with progressive MS.

Recently, several groups have treated patients with MS with more aggressive immune system ablation, requiring autologous hematopoietic progenitor rescue. In the majority of these studies, there was an apparent improvement or stabilization of the clinical course. Additionally, standard magnetic resonance imaging (MRI) measures of disease activity have shown dramatic, if not complete, stabilization with such regimens. In several patients, long-term remission of both inflammation and progression was achieved. However, some patients developed accelerated brain atrophy as a result of the conditioning regimen and transplant-related mortality in such patients was between 5% and 15%. Despite its immunoablative properties, high doses (120–200 mg/kg) of Cy (HiCy) used as conditioning for transplant is well tolerated and spares hematopoietic stem cells, as demonstrated by rapid hematopoietic recovery and immune reconstitution following this treatment in patients with severe autoimmune diseases. The major mechanism of Cy detoxification is inactivation of aldehyd e dehydrogenase by cellular aldehyde dehydrogenase to form the inert compound carboxyphosphamide. Aldehyde dehydrogenase is highly expressed in hematopoietic stem cells, whereas all mature or maturing cells, including lymphocytes, express relatively low levels of aldehyde dehydrogenase and are therefore rapidly eliminated by HiCy. Recently, 13 patients with severe refractory MS (7 with secondary progressive MS and 6 with relapsing–remitting MS) were studied following treatment with HiCy, and many were found to have stabilization or improvement of disability. All reported an improvement in quality-of-life measures.

In our study, HiCy treatment without hematopoietic stem cell transplantation was studied in patients with severe MS. This study examined radiologic and clinical features not previously studied and had a longer follow-up (23 months) than previously published. We found that HiCy treatment induced a significant reduction in disease activity and disability in most patients. Some patients experienced sustained remission of all detectable disease activity despite receiving no subsequent immunomodulatory therapy.

**STUDY DESIGN AND INCLUSION CRITERIA**

A total of 21 patients were screened for eligibility and 9 were enrolled between October 2003 and July 2006. Men and women between the ages of 18 and 70 years who had failed or refused conventional therapy and had active disease were enrolled. Active disease was defined as 1 clinical exacerbation between 6 and 12 months prior to HiCy treatment or a sustained increase in more than 1 Expanded Disability Status Scale (EDSS) point in the past year and 2 or more gadolinium-enhancing lesions (GELs) on each of 2 pretreatment MRI scans. Patients were excluded if they had a clinical exacerbation within 3 months prior to administration of HiCy, as those patients might not have had stable disability. These criteria were designed to identify a patient population with ongoing inflammatory disease activity, high risk of continued progression, and loss of function.

**STUDY TREATMENT**

Approval from the Johns Hopkins institutional review board was obtained. Patients gave consent twice, at screening and prior to enrollment into the study if they met all inclusion criteria. All patient case summaries were presented to a steering committee to ensure by unanimous approval that they met all inclusion criteria and no exclusion criteria. Pretreatment studies included electrocardiogram, echocardiogram or multiple gated acquisition scan, sinus computed tomography, and extensive blood work.

Patients received 50 mg/kg/d of Cy intravenously for 4 consecutive days. The dose of Cy was calculated according to ideal body weight. Prophylaxis against Cy-induced hemorrhagic cystitis (generally Mesna [Uromitexan; Baxter, Deerfield, Illinois]) was directed according to established clinical practice guidelines. On day 6 (6 days after completion of HiCy treatment) all patients received 5 µg/kg/d of the myeloid growth factor filgrastim (granulocyte colony–stimulating factor) until the absolute neutrophil count exceeded 1.0 × 109 cells/L for 2 consecutive days. Patients also routinely received prophylactic antibiotics (norfloxacin, fluconazole, and valacyclovir) while granulocytopenic.

**OUTCOME MEASURES**

Patients were evaluated at the Johns Hopkins General Clinical Research Center every 3 months. Evaluations included standard blood profile, urinalysis, electrocardiogram, echocardiogram, neurologic examination, and MRI evaluations. Disability was measured using the EDSS and Multiple Sclerosis Functional Composite (MSFC).

Magnetic resonance imaging scans were performed at 1.5 T (General Electric, Milwaukee, Wisconsin) with an echo speed or twin speed gradients, using the Excite platform (General Electric Healthcare, Chalfont St Giles, United Kingdom). Magnetic resonance imaging pulse sequences included axial proton density T2-weighted combined pulse sequence, fluid-attenuated inversion recovery sequences, and axial pregadolinium and postgadolinium T1-weighted scans (0.2 mmol/kg...
using Omniscan [General Electric Healthcare]; this is double the dose compared with conventional scanning protocols. ²⁸

**STATISTICAL ANALYSIS**

Statistical tests were performed using SPSS 15.0 (SPSS, Chicago, Illinois). Although 2 patients received other immunomodulatory treatments during follow-up, all patients were followed up for safety and included in the effectiveness analysis (intention-to-treat analysis). Means, medians, and standard deviations were calculated. Nonparametric tests (Wilcoxon rank sum test) were used to evaluate the change at follow-up compared with baseline. The MSFC z-scores were calculated using a standardized reference population from the National Multiple Sclerosis Society Task Force data set. ²⁷ ²⁸ Baseline EDSS and MSFC scores were used to calculate the percentage of change in disability scores at follow-up. The screening data were used for patient 5, as the baseline MSFC visit was missing.

**MRI ANALYSIS**

Brain parenchymal fraction (BPF) was computed as the ratio of brain volume to intracranial volume, as previously described. ²⁹ The T2 plaque volumes were semiautomatically obtained using a fuzzy segmentation procedure ³⁰ ³¹ applied to the brain-extracted fluid-attenuated inversion recovery images by modeling plaque intensities as outliers, similar to the approach described by Van Leemput et al. ³² The resulting segmentation was inclusive of the plaques but included false-positives that were manually removed by a trained operator using information from both the fluid-attenuated inversion recovery and T2-weighted scans. Changes in lesion volume were measured on T2-weighted images from baseline to the most recent follow-up visit, and annualized changes in BPF were calculated using the Wilcoxon signed rank test.

**RESULTS**

**DEMOGRAPHICS**

The baseline demographic characteristics of this study population (6 men, 3 women; mean [SD] age at entry, 35 [3.5] years) are described in Table 1. There were 3 African American patients (patients 5, 7, and 9). The mean disease duration was 7.6 years (median, 4 years; range, 1.5-15 years). This cohort had a baseline annualized relapse rate of 1.7 episodes per year (historical data), a mean EDSS score of 5.0, and a mean (SD) of 6.5 (2.1) GELs using double-dose gadolinium (Table 1). Eight patients had failed conventional immunomodulatory therapy and 1 patient was treatment naive at entry. The mean time to follow-up after HiCy treatment in this cohort was 23 months.

**HEMATOLOGIC RECOVERY**

The total white blood cell count fell to fewer than 80 cells/mm³ in all patients, with recovery measuring more than 3500 cells/mm³ at a median of 15 (range, 13-30) days after the last dose of Cy (Figure 1). The median number of red blood cell transfusions was 2 (range, 0-4), and the median number of platelet transfusions was 1 (range, 0-3).

**SAFETY**

High-dose cyclophosphamide was well tolerated, with no serious or unexpected adverse events. Two patients developed febrile neutropenia, and 3 had self-limited documented infections. There was 1 episode of confusion (patient 3) at 15 months that was probably unrelated to the HiCy treatment. The patient was also taking lithium and amitriptyline and had not decreased his dose as suggested by his physician. There were 4 hospital or emergency department admissions during the study follow-up. Patient 1 was admitted to the hospital on 2 occasions owing to suspected MS exacerbation that was not confirmed by MRI. The patient was treated with rituximab 10 months after HiCy treatment and pulse cyclophosphamide at month 12. The patient’s EDSS score was 7.0 at 9 months and 8.0 at the 12-month follow-up visit. The EDSS score had decreased to 7.5 at 15 months. Although there was no clear change in the patient’s disability immediately after either

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**Table 1. Demographic Characteristics and Disease History**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y, at Entry Into Study</th>
<th>Disease Duration, y</th>
<th>Annualized Relapse Rate</th>
<th>Pretreatment Baseline EDSS Score</th>
<th>Baseline Average No. of Enhancing Lesions (2 Pretreatment Scans)</th>
<th>Past Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/47</td>
<td>15</td>
<td>1.5</td>
<td>7.0</td>
<td>4.5</td>
<td>Steroids, Avonex,³² Rebi³ IVIG, pulse cyclophosphamide</td>
</tr>
<tr>
<td>2/M/46</td>
<td>9</td>
<td>1.17</td>
<td>7.0</td>
<td>5.5</td>
<td>Steroids, Avonex</td>
</tr>
<tr>
<td>3/M/27</td>
<td>2</td>
<td>1.67</td>
<td>5</td>
<td>8</td>
<td>Rebi⁴, Avonex, steroids</td>
</tr>
<tr>
<td>4/F/46</td>
<td>15</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>Avonex, steroids, glatiramer acetate</td>
</tr>
<tr>
<td>5/F/44</td>
<td>15</td>
<td>1.33</td>
<td>6.5</td>
<td>9</td>
<td>Steroids, Betaseron,⁵ Rebi⁴, glatiramer acetate</td>
</tr>
<tr>
<td>6/M/28</td>
<td>3</td>
<td>3</td>
<td>3.5</td>
<td>6.5</td>
<td>Rebi, glatiramer acetate</td>
</tr>
<tr>
<td>7/M/29</td>
<td>4</td>
<td>1.5</td>
<td>1.5</td>
<td>7</td>
<td>Avonex, steroids, Cellcept⁶</td>
</tr>
<tr>
<td>8/M/28</td>
<td>1.5</td>
<td>1.5</td>
<td>4.5</td>
<td>6</td>
<td>No treatment</td>
</tr>
<tr>
<td>9/F/29</td>
<td>4</td>
<td>1.8</td>
<td>6.5</td>
<td>3.5</td>
<td>Steroids, Avonex</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; IVIG, intravenous immunoglobulin; HiCy, high-dose cyclophosphamide.

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of these treatments, he did have an improvement; his symptoms were back to baseline by the completion of the study. Patient 5 had a clinical exacerbation 4 days prior to her scheduled 18-month visit and was treated with steroids. Her baseline EDSS score was 6.5 and she had an average of 9 GELs prior to HiCy treatment. At 18 months, her EDSS score was 3.5. She developed mild truncal ataxia and recurrence of fatigue that had been debilitating prior to HiCy treatment. Her MRI revealed 3 possible lesions with weak gadolinium enhancement, and she started an intravenous steroid regimen, resulting in some improvement, followed by ongoing monthly daclizumab therapy. At her 24-month follow-up, she had an EDSS score of 3.5 and 1 GEL on her MRI.

Patient 9 was admitted to the emergency department at 12 months, following a motor vehicle crash. She developed a urinary tract infection, resulting in an increase in her EDSS score at 12 months. Patient 7 had a hospital admission at 19 months owing to confusion and cognitive changes and was diagnosed with bipolar affective disorder.

**DISABILITY (EDSS AND MSFC SCORES)**

The mean (SD) baseline EDSS score of the cohort was 5.17 (1.84) (range, 1.5-7.0). Patients 1 and 2 worsened by 0.5 point on the EDSS between screening and baseline; this protocol deviation was reported to the institutional review board. At the last evaluation, the mean (SD) EDSS score for all patients in the study was 3.06 (2.36) (range, 0-7; P = .02). This represents an aggregate 39.4% reduction in disability in an average follow-up of 23 months. Individual EDSS scores at baseline and follow-up are shown in Table 2. Four of the patients had no change or less than a 1-point change on the EDSS at the last follow-up from baseline, while 5 had a sustained decrease of greater than 1 point on the EDSS that persisted through the last examination. In the subgroup of patients who improved by more than 1 EDSS point at the last follow-up, there was a 65% reduction in EDSS scores.

Patients were administered the MSFC, a multidimensional clinical outcome measure that measures upper extremity, lower extremity, and cognitive function at screening, baseline, and at each study visit at 3-month intervals under standardized conditions. The baseline scores were used to calculate the MSFC $z$ scores, to account for practice effects. The cohort had a statistically significant improvement in MSFC $z$ scores (average improvement, 87%; $P = .03$). The improvement was noted in all 3 of the MSFC subscores, although a change in the 9-Hole Peg Test score did not reach statistical significance (Table 3). At baseline, patient 9 was unable to complete the Timed 25-Foot Walk within 3 minutes. By the 3-month follow-up, the time to complete the Timed 25-Foot Walk was 6.5 seconds, and at 12 months it was 4.9 seconds.
The mean (SD) number of GELs at baseline was 6.5 (2.1) (range, 2-11) at screening and baseline. At the last follow-up, there were a mean (SD) of 1.2 (2.3) (range, 0-7), representing an 81% reduction ($P=0.01$).

Figure 2 graphically depicts each patient’s treatment response (baseline visit prior to treatment with HiCy is time 0) as the change in EDSS scores and number of GELs at each point assessed during the course of the study. Three patients had a recurrence of clinically silent radiological disease activity, as defined by the presence of new GELs after achieving complete cessation of GELs following HiCy treatment that did not correlate with a clinical exacerbation or worsening of disability (patients 3, 6, and 7). Patients 5 and 9 continued to have GELs at and beyond 6 months after HiCy therapy.

The T2 lesion burden was assessed at baseline and at the last follow-up. The change in the total volume of T2 burden was $-0.93\%$ at an average follow-up of 22.1 months ($P=0.05$). Four patients had a reduction in T2 plaque burden.

### Table 2. Change in Disability (EDSS Score) at 12-Month Follow-up and Last Follow-up

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Follow-up, mo</th>
<th>Pretreatment</th>
<th>12-Month Follow-up</th>
<th>Last Follow-up</th>
<th>Change at Last Follow-up, %a</th>
<th>Change at Last Follow-up, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>7.0</td>
<td>8.0</td>
<td>6.5</td>
<td>$-0.5$</td>
<td>$-7.14$</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>7.0</td>
<td>8.0</td>
<td>7.0</td>
<td>$0.0$</td>
<td>$0.0$</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>5.0</td>
<td>1.0</td>
<td>3.0</td>
<td>$-2.0$</td>
<td>$-40.0$</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>5.0</td>
<td>0.0</td>
<td>0.0</td>
<td>$-5.0$</td>
<td>$-100.0$</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>6.5</td>
<td>3.0</td>
<td>3.5</td>
<td>$-3.0$</td>
<td>$-46.2$</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>3.5</td>
<td>3.0</td>
<td>3.0</td>
<td>$-0.5$</td>
<td>$-14.3$</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>$0.0$</td>
<td>$0.0$</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>4.5</td>
<td>1.0</td>
<td>1.0</td>
<td>$-3.5$</td>
<td>$-77.8$</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>6.5</td>
<td>1.0</td>
<td>2.0</td>
<td>$-4.5$</td>
<td>$-69.2$</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23</td>
<td>5.17 (1.84)</td>
<td>2.94 (3.03)</td>
<td>3.06 (2.36)</td>
<td>$-2.11$ (1.97)</td>
<td>$-39.4$</td>
</tr>
</tbody>
</table>

Abbreviation: EDSS, Expanded Disability Status Scale.

a Patient 9 has completed 15-month follow-up.

b $P=0.02$ (Wilcoxon rank sum test).

### Table 3. Change in Each Component of MSFC (z Score) From Baseline

<table>
<thead>
<tr>
<th>Component</th>
<th>Baseline (n=9)</th>
<th>Last Follow-up (n=9)</th>
<th>Mean Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T25FW</td>
<td>Mean (SD)</td>
<td>$-4.91$ (6.77)</td>
<td>$-2.75$ (6.21)</td>
<td>2.16</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>$-13.7$ to 0.45</td>
<td>$-13.7$ to 0.51</td>
<td></td>
</tr>
<tr>
<td>9HPT</td>
<td>Mean (SD)</td>
<td>$-1.82$ (1.86)</td>
<td>$-0.97$ (1.84)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>$-4.22$ to 0.71</td>
<td>$-3.91$ to 1.05</td>
<td></td>
</tr>
<tr>
<td>PASAT3</td>
<td>Mean (SD)</td>
<td>$-1.38$ (1.43)</td>
<td>$-0.40$ (1.28)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>$-3.73$ to 0.33</td>
<td>$-2.49$ to 1.24</td>
<td></td>
</tr>
<tr>
<td>MSFC</td>
<td>Mean (SD)</td>
<td>$-2.70$ (2.86)</td>
<td>$-1.38$ (2.76)</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>$-7.22$ to 0.16</td>
<td>$-6.25$ to 0.71</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 9HPT, 9-Hole Peg Test; MSFC, Multiple Sclerosis Functional Composite; PASAT3, Paced Auditory Serial Addition Test with 3-second interstimulus interval; T25FW, Timed 25-Foot Walk.

a Wilcoxon signed rank test.

**RADIOLOGICAL MEASURES**

The mean (SD) number of GELs at baseline was 6.5 (2.1) (range, 2-11) at screening and baseline. At the last follow-up, there were a mean (SD) of 1.2 (2.3) (range, 0-7), representing an 81% reduction ($P=0.01$). Figure 2 graphically depicts each patient’s treatment response (baseline visit prior to treatment with HiCy is time 0) as the change in EDSS scores and number of GELs at each point assessed during the course of the study. Three patients had a recurrence of clinically silent radiological disease activity, as defined by the presence of new GELs after achieving complete cessation of GELs following HiCy treatment that did not correlate with a clinical exacerbation or worsening of disability (patients 3, 6, and 7). Patients 5 and 9 continued to have GELs at and beyond 6 months after HiCy therapy.

The T2 lesion burden was assessed at baseline and at the last follow-up. The change in the total volume of T2 burden was $-0.93\%$ at an average follow-up of 22.1 months ($P=0.05$). Four patients had a reduction in T2 plaque burden.

Brain parenchymal fraction was measured at baseline, 3 months, and from follow-up to 24 months in 8 patients (Table 4). We first measured changes in the BPF between baseline and the 3 months after the HiCy MRI to determine whether HiCy treatment induced any accelerated atrophy (Table 4). There was a $-2.4\%$ change (annualized change, $-9.4\%$) in BPF between baseline (prior to acute therapy) and 3 months after treatment with HiCy (median BPF at baseline, 0.807; range, 0.75-0.87 vs median BPF at 3 months, 0.797; range, 0.70-0.86; $P=0.01$). There was no statistically significant difference at follow-up (mean, 23 months) in the annualized change in BPF ($-0.23\%$; $P=0.05$) when compared with the MRI 3 months after HiCy treatment. This suggests that the reduction in BPF associated with HiCy treatment may reflect the resolution of inflammation (pseudoatrophy).

**COMMENT**

High-dose cyclophosphamide treatment of patients with aggressive MS was safe and well tolerated and did not lead...
to excess morbidity or accelerated brain atrophy. Moreover, HiCy induced a functional improvement in most of the patients we studied. In many of those patients, the functional improvement was sustained through the length of the study (up to 24 months) despite the absence of any immunomodulatory therapies beyond the initial HiCy.

Table 4. Change in Brain Atrophy Measures

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>21</th>
<th>24</th>
<th>Annualized Change From Baseline to 3 mo, %</th>
<th>Annualized Change, Follow-up vs Baseline, %</th>
<th>Annualized Change, Follow-up vs 3 mo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–23.717</td>
<td>–4.566</td>
<td>–1.946</td>
</tr>
<tr>
<td>2</td>
<td>0.747</td>
<td>0.703</td>
<td>0.705</td>
<td>b</td>
<td>0.694</td>
<td>0.679</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.860</td>
<td>0.827</td>
<td>0.825</td>
<td>0.849</td>
<td>0.827</td>
<td>0.838</td>
<td>−15.064</td>
<td>–1.259</td>
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<td>4</td>
<td>0.803</td>
<td>0.781</td>
<td>0.798</td>
<td>0.776</td>
<td>0.784</td>
<td>0.789</td>
<td>−10.755</td>
<td>−0.876</td>
<td>0.550</td>
</tr>
<tr>
<td>5</td>
<td>0.801</td>
<td>0.796</td>
<td>0.795</td>
<td>0.808</td>
<td>0.809</td>
<td>0.808</td>
<td>−2.442</td>
<td>0.409</td>
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<td>6</td>
<td>0.830</td>
<td>0.821</td>
<td>0.816</td>
<td>0.820</td>
<td>0.828</td>
<td>0.800</td>
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<td>–1.842</td>
<td>–1.471</td>
</tr>
<tr>
<td>7</td>
<td>0.812</td>
<td>0.798</td>
<td>0.794</td>
<td>0.784</td>
<td>0.784</td>
<td>0.775</td>
<td>−7.252</td>
<td>–2.283</td>
<td>–1.603</td>
</tr>
<tr>
<td>8</td>
<td>0.870</td>
<td>0.861</td>
<td>0.838</td>
<td>0.862</td>
<td>0.859</td>
<td>0.863</td>
<td>−4.572</td>
<td>–0.408</td>
<td>0.189</td>
</tr>
<tr>
<td>9</td>
<td>0.795</td>
<td>0.781</td>
<td>0.787</td>
<td>0.787</td>
<td></td>
<td></td>
<td>−6.883</td>
<td>–1.054</td>
<td>0.905</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.815 (0.039)</td>
<td>0.796 (0.046)</td>
<td>0.795 (0.040)</td>
<td>0.812 (0.033)</td>
<td>0.798 (0.053)</td>
<td>0.793 (0.059)</td>
<td>−9.4d</td>
<td>−1.49e</td>
<td>−0.23</td>
</tr>
</tbody>
</table>

aChange at last available follow-up data.
bData unavailable owing to motion artifact.
cOnly screening measure available for patient 2.
dP < .01.
eP < .02.
treatment. Three patients had radiologic reactivation of disease at various intervals after treatment with HiCy, and 1 patient had clinical and radiologic reactivation, suggesting that disease remission may only be transient in some patients.

The complexity of the autoimmune response in MS presents a critical strategic problem. Because individual MS patients may have distinct autoimmune effector mechanisms, highly specific targeted immunotherapies may be effective only for subsets of patients with MS. The activity of HiCy does not require identifying, targeting, and eliminating each individual’s unique aberrant immune repertoire because of its activity against all arms of an immunologic response. Ideally, the goal of HiCy therapy is to ablate virtually the entire mature immune system, including the autoimmune component, allowing the individual’s immune system to be reconstituted from the undamaged stem cell population. If this is achieved, the new immune system should recognize and become tolerant of the antigens present, including those that previously contributed to the autoimmune process.2535

We studied HiCy therapy in a cohort of patients with aggressive, inflammatory MS for several reasons. First, because this was a pilot study of HiCy treatment in MS, we wanted to explore only those patients who had worsening disease while receiving conventional therapies. Second, we reasoned that patients with active inflammatory disease would be more likely to respond to HiCy therapy than those with later-stage MS and more limited inflammation. Finally, we reasoned that such patients might have more reversible disability than those with later stages of the disease.

Treatment with HiCy not only halted the accrual of disability that occurred prior to HiCy treatment but also stably reduced this disability in many of the patients. We suggest that the total disability in these patients is contributed by demyelination, axonal injury, and ongoing inflammation. Cessation of active inflammation by HiCy ablation might facilitate a permissive environment for reparative plasticity in the central nervous system that could account for some of the clinical improvement we observed. In this context, the 2 patients who had had a high level of sustained disability (patients 1 and 2; EDSS score, 7.0) did not experience a modest improvement in MSFC score. Perhaps this is suggestive of a limited window during which endogenous central nervous system reparation is viable. Therefore, it is unclear if patients with this high level of disability are the optimal cohort to study further because their response to therapy was more modest.

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REFERENCES


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