Immune Reconstitution Inflammatory Syndrome in Patients With Multiple Sclerosis Following Cessation of Natalizumab Therapy

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**Objective:** To assess clinical consequences of temporary natalizumab dosage suspension.

**Design:** Prospective cohort study.

**Setting:** Multiple sclerosis (MS) center at an academic medical center in the United States.

**Patients:** Thirty-two patients with MS who had received at least 12 consecutive natalizumab infusions.

**Main Outcomes Measures:** Recurrent MS disease activity, defined as a clinically documented exacerbation with objective findings and/or the development of 1 or more new gadolinium-enhancing lesions on magnetic resonance imaging.

**Results:** Thirty-eight percent of patients with relapsing-remitting and secondary progressive MS experienced relapses during therapy interruption or shortly after restarting natalizumab therapy (9 of 24 and 3 of 8, respectively), but relapses were severe with unusually widespread evidence of inflammatory activity on magnetic resonance imaging in several patients with secondary progressive MS with greater inflammatory disease activity prior to starting natalizumab therapy. Imaging and cerebrospinal fluid findings in these cases were suggestive of an immune reconstitution inflammatory syndrome. Overall, relapses occurred more often in younger patients with fewer natalizumab infusions prior to therapy interruption. The number of gadolinium-enhancing lesions at the time of relapse after therapy interruption was modestly correlated with the number of gadolinium-enhancing lesions prior to starting natalizumab therapy ($r = 0.51; P = .45$). Prior disease control resumed after re-institution of natalizumab therapy in all patients.

**Conclusions:** In this cohort of patients with MS who had disease refractive to multiple therapeutics before starting natalizumab treatment, magnetic resonance imaging and clinical disease activity returned, often aggressively, following discontinuation of natalizumab therapy. These findings suggest we should consider strategies to minimize the risk of immune reconstitution inflammatory syndrome after natalizumab discontinuation.


Natalizumab, a humanized monoclonal antibody against $\alpha_4$ integrin, has been shown to significantly reduce the rate of clinical relapse, the development of T2 and gadolinium-enhancing magnetic resonance imaging (MRI) lesions, and the progression of disability in patients with relapsing forms of multiple sclerosis (MS). There have been more than 50 cases of progressive multifocal leukoencephalopathy (PML) in patients with MS receiving natalizumab, all developing after at least 1 year of therapy. Evidence suggests that the risk of developing PML is higher with prolonged periods of immunosuppression. In an attempt to periodically restore normal immune surveillance and decrease the risk of PML, we instituted a 3- to 4-month drug holiday for all patients who had received at least 12 consecutive natalizumab infusions at Beth Israel Deaconess Medical Center. We selected the duration of our drug holiday on the basis of pharmacokinetic and pharmacodynamic studies suggesting that the very late antigen 4 blockade persists for up to 2 to 3 months after an infusion. Although a phase 2 study of natalizumab treatment for 6 months suggested a return of clinical and MRI disease activity within 6 months of cessation of therapy, there was no suggestion of a rebound increase in clinical or MRI activity compared with the placebo.
control group. Another study reported a continued reduction in clinical and radiologic disease activity compared with pretreatment in 23 patients for up to 14 months after cessation of therapy, but most patients began alternative disease-modifying therapy after stopping natalizumab treatment. The only study suggesting a rebound increase in MRI activity following cessation of natalizumab therapy relied solely on nonenhanced MRI scans obtained 15 months after stopping natalizumab therapy.

This study reported a significant increase in new or enlarging T2 lesions compared with the pretreatment period, primarily in those patients with a short duration of natalizumab therapy (median, 2 infusions; range, 1–8 infusions). Taken together, these studies suggested that temporary cessation of natalizumab therapy for 3 to 4 months in patients receiving prolonged uninterrupted therapy would not be associated with worsening disease activity and may restore immune surveillance.

The aim herein is to report the clinical outcome of 32 patients with relapsing-remitting (RRMS) and secondary progressive MS (SPMS) after discontinuation of long-term natalizumab therapy.

All of our patients with MS receiving natalizumab therapy at Beth Israel Deaconess Medical Center for at least 12 consecutive months (N=32) by August 29, 2008, underwent a planned, voluntary, 3- to 4-month dosage suspension without intervening treatment. All dosage suspensions began between July 1, 2008, and August 30, 2008. The protocol was initiated after further reports of PML in the press led a majority of our patients to express concern about continuing to receive therapy beyond 12 months. All patients agreed to this temporary cessation of therapy intended to restore normal immune surveillance and decrease the risk of PML. The duration of the voluntary dosage suspension was chosen to minimize the risk of recurrent relapses based on previously reported studies (see earlier). The protocol was discontinued in late October 2008, initially because of patient self-report of worsening MS symptoms and subsequently because of an unexpected frequency of relapses earlier than 6 months following dosage cessation. The protocol was based on customary practice and retrospective analysis of the data collected was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation.

Recurrence MS disease activity was defined as a clinically documented exacerbation with objective findings and/or the development of new gadolinium-enhancing lesions on MRI. Most patients underwent standard cranial MRI with and without gadolinium prior to starting natalizumab therapy (31 of 32), after 1 year of natalizumab therapy (30 of 32), and at the end of their therapy interruption (29 of 32) period as part of our standard protocol. Baseline MRI scans were obtained either prior to initiation of corticosteroid use or at least 1 month after completion of corticosteroid use. All patients were negative for antinatalizumab antibodies after 1 year of therapy. The MRI results were interpreted by a neuroradiologist who counted the number of enhanced lesions following the administration of gadolinium. Images were reanalyzed by a blinded investigator during retrospective review to confirm gadolinium lesion counts in comparison with preenhanced T1-weighted images. Spinal fluid analysis was done to exclude PML-associated immune reconstitution inflammatory syndrome (IRIS) in selected cases. A Pearson correlation coefficient was calculated to compare the association between the number of gadolinium-enhancing lesions before and after the natalizumab holiday. Mean gadolinium-enhancing lesion counts before and after the natalizumab holiday were compared by generalized estimating equations using a negative binomial distribution with an unstructured working correlation matrix.

Thirty-two patients (SPMS, n=8; RRMS, n=24) receiving natalizumab therapy for a period longer than 12 consecutive months (mean, 17.3 months) underwent a voluntary dosage suspension. During that period, none of our patients received any other disease-modifying therapies for the treatment of MS other than high-dose corticosteroids for relapses. The characteristics of the study patients are provided in Table 1. All patients were receiving 1 or more standard disease-modifying therapies prior to initiation of natalizumab therapy and most (72%) had received more than 1 disease-modifying therapy or immunosuppressant therapy in the past. Only 3 patients primarily switched to natalizumab therapy because of an inability to tolerate disease-modifying therapies (1 experienced a relapse during natalizumab therapy interruption and 2 did not). Based on pre–natalizumab therapy relapse counts (mean [SD], 1.3 [1.1] and 2.3 [1.5] relapses in previous 1 and 2 years, respectively) and baseline gadolinium-enhancing lesion counts (mean [SD], 1.9 [2.9]) despite receiving standard disease-modifying therapy, this was a cohort of patients with active relapsing MS poorly responsive to standard disease-modifying therapy.

The mean (SD) duration of therapy interruption was 119.2 (29.1) days or approximately 4 months. All patients restarted therapy within 6 months of therapy interruption (71% within 120 days) except for 1 patient who chose not to restart therapy. Clinically defined relapses occurred in 38% (9 of 24) of the RRMS group and 25% (2 of 8) of the SPMS group during their period of therapy interruption. Nine of the 11 relapses were at least moderate in severity (altered functional status). The recurrent MRI disease activity was concurrently associated with clinical relapse in all but 1 of the patients (patient 1; Table 2). Patient 1 experienced increased fatigue and complained of worsening cognition within 100 days of therapy interruption and was found to have 3 gadolinium-enhancing lesions 100 days after the last dose of natalizumab. The patient subsequently experienced a severe relapse requiring hospitalization exactly 1 month after restarting natalizumab therapy during which time the patient was noted to have 37 gadolinium-enhancing lesions and no evidence of antinatalizumab antibodies (Figure). The 3 patients with RRMS without cranial gadolinium-enhancing lesions all experienced relapses confirmed by MRI that were confined to the spinal cord. Spinal fluid analysis (Table 2) was done in 3 patients for atypical features including a progressive homonymous hemianopsia (1), cognitive worsening with fatigue (1), and an atypical MRI appearance (1). This revealed a lymphocytic pleocytosis, with normal glucose level, protein level, and culture results. Results of a polymerase chain reaction test for JC virus were negative in all 3 patients.
Patients who experienced a relapse during therapy interruption tended to be younger (mean age, 32.5 vs 40.6 years; \( P = .06 \)) with a shorter duration of natalizumab treatment prior to therapy interruption (mean number of infusions, 15.3 vs 18.5; \( P = .02 \)). There was a trend suggesting a higher pretherapy relapse count (mean relapses in previous year, 1.7 vs 1.2; \( P = .19 \)) in those who experienced a relapse during treatment interruption. Similarly, the 2 patients experiencing relapses during natalizumab therapy both experienced relapses during their interruption in therapy. Post–natalizumab therapy interruption MRI activity (number of gadolinium-enhancing lesions) in those patients who experienced a relapse was modestly correlated with the number of gadolinium-enhancing lesions before natalizumab treatment (\( r = 0.51 \); 1-tailed \( P \) value = .043), suggesting that those patients with greater MRI disease activity before natalizumab treatment experience greater MRI disease activity after natalizumab treatment. The relationship was unidirectional, with all but 1 patient experiencing more gadolinium-enhancing lesions after voluntary discontinuation. The mean (SD) number of gadolinium-enhancing lesions prior to starting natalizumab therapy (9.5 [12.4] vs 2.0 [2.6]; \( P < .001 \)) in patients experiencing a relapse, with an estimated increase of 4.8 gadolinium-enhancing lesions. Although our study design does not allow for a definitive conclusion, the number of gadolinium-enhancing lesions postinterruption, and thus the extent of inflammatory response, seem to increase with the duration of time between therapy interruption and relapse/MRI (Table 2). The remaining 20 patients without a relapse had either no gadolinium-enhancing lesions (\( n = 17 \)) or did not undergo a post–therapy interruption MRI (\( n = 3 \)).

Forty-two percent (5 of 12) of patients experienced only partial recovery from their relapse during the drug holiday but no patient still in follow-up (0 of 31) experienced a relapse or MRI activity (0 of 23 with a follow-up MRI at 1 year) up to 1 year since restarting natalizumab therapy. Eighty-four percent of all patients (27 of 32) and 83% (10 of 12) of those with relapses during therapy interruption have continued receiving natalizumab therapy for more than a year since restarting treatment. Two patients discontinued therapy because of a continued progressive course, including patient 4, who was classified as having RRMS before therapy interruption. One patient who did well during therapy interruption discontinued natalizumab therapy out of concern for

Table 1. Characteristics of Study Patients by Therapy Interruption Outcome (Relapse vs No Relapse)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (( N = 32 ))</th>
<th>Patients With Relapse During Treatment Interruption (( n = 12 ))</th>
<th>Patients With No Relapse During Treatment Interruption (( n = 20 ))</th>
<th>( P ) Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>37.6 (11.7)</td>
<td>32.5 (11.0)</td>
<td>40.6 (11.3)</td>
<td>.056</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>21 (66)</td>
<td>8 (67)</td>
<td>13 (65)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>MS duration, y, mean (SD)</td>
<td>9.4 (5.8)</td>
<td>6.0 (6.7)</td>
<td>8.7 (5.3)</td>
<td>.19</td>
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<tr>
<td>Disease type, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPMS</td>
<td>8 (25)</td>
<td>3 (25)</td>
<td>5 (25)</td>
<td>&gt; .99</td>
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<tr>
<td>RRMS</td>
<td>24 (75)</td>
<td>9 (75)</td>
<td>15 (75)</td>
<td>.76</td>
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<tr>
<td>EDSS score, mean (SD)</td>
<td>3.3 (1.9)</td>
<td>3.4 (1.6)</td>
<td>3.3 (2.1)</td>
<td>.81</td>
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<tr>
<td>Relapses, mean (SD)</td>
<td></td>
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<tr>
<td>1 y prior</td>
<td>1.3 (1.1)</td>
<td>1.7 (1.2)</td>
<td>1.2 (1.0)</td>
<td>.19</td>
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<tr>
<td>2 y prior</td>
<td>2.3 (1.5)</td>
<td>2.6 (1.4)</td>
<td>2.1 (1.5)</td>
<td>.34</td>
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<tr>
<td>Gd+ lesions, No. (%)</td>
<td></td>
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<tr>
<td>0</td>
<td>14 (45)</td>
<td>5 (45)b</td>
<td>9 (45)</td>
<td>.71</td>
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<td>1-2</td>
<td>11 (35)</td>
<td>3 (27)</td>
<td>8 (40)</td>
<td>.73</td>
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<td>( \geq 3 )</td>
<td>6 (19)</td>
<td>3 (27)</td>
<td>3 (15)</td>
<td>.73</td>
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<td>Prior MS treatments, ( \geq 3 ) No. (%)</td>
<td></td>
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<tr>
<td>1</td>
<td>9 (28)</td>
<td>3 (25)</td>
<td>6 (30)</td>
<td>.73</td>
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<tr>
<td>2</td>
<td>13 (41)</td>
<td>6 (50)</td>
<td>7 (35)</td>
<td>.73</td>
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<tr>
<td>( \geq 3 )</td>
<td>10 (31)</td>
<td>3 (25)</td>
<td>7 (35)</td>
<td>.73</td>
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Abbreviations: EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

a\( P \) values comparing patients with a relapse during treatment interruption with patients without relapse during treatment interruption (from a \( t \) test for means or from a Fisher exact test for proportions).

bOne patient did not have a baseline magnetic resonance image immediately prior to onset of natalizumab therapy.

Prior MS treatments included interferon beta-1a (Avonex, Betaseron, and Rebif), glatiramer acetate (Copaxone), bimonthly high-dose methylprednisolone treatments, monthly high-dose cyclophosphamide treatments, monthly immunoglobulin infusions, methotrexate, and azathioprine.
the increasing risk of PML with longer treatment duration; another patient discontinued natalizumab therapy for pregnancy; and the last patient was lost to follow-up 6 months after drug holiday and never restarted therapy. Forty percent of all patients (13 of 32) retrospectively reported that they would be very reluctant to consider another interruption in natalizumab therapy without alternative treatment.

In view of the continued reports of the rare occurrence of patients developing PML during natalizumab therapy, it is imperative to understand the clinical consequences of therapy discontinuation. Previous reports of outcomes after discontinuation of therapy suggested an eventual return of disease activity to pretreatment levels over 6 months but no evidence of rebound, with the possible exception of those patients stopping natalizumab therapy after a shorter treatment duration.\(^5\) Our cohort of 32 patients experienced near complete cessation of MRI and clinical disease activity, as well as significant improvement in daily symptoms, during natalizumab therapy even though they represent a group of patients who had disease refractive to multiple therapeutics before starting treatment. One-third of our patients who had disease refractive to multiple therapeutics before starting treatment. One-third of our patients who had disease refractive to multiple therapeutics before starting treatment. One-third of our patients who had disease refractive to multiple therapeutics before starting treatment. One-third of our patients who had disease refractive to multiple thera-

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Table 2. Pre– and Post–Natalizumab Therapy Outcomes in Patients With Disease Activity During Treatment Interruption

| Patient No./ MS Type | No. of Gd+ Lesions Pretreatment | No. of New T2/Gd+ Lesions at 1 y of Treatment | No. of Infusions Before Interruption | Time to Relapse, Days Since Therapy Interruption | No. of Gd+ Lesions After Therapy Interruption | Relapse CSF WBC Count | Relapse Outcome/ Course 1 y After Restarting Nata
dizumab Therapy |
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<td></td>
<td></td>
</tr>
<tr>
<td>1/SP</td>
<td>8</td>
<td>0/0</td>
<td>17</td>
<td>1st: 100(^1)</td>
<td>1st: 2(^2)</td>
<td>9</td>
<td>Incomplete recovery/stable</td>
</tr>
<tr>
<td>2/SP</td>
<td>2</td>
<td>0/0</td>
<td>12</td>
<td>120</td>
<td>14</td>
<td></td>
<td>Incomplete recovery/progression</td>
</tr>
<tr>
<td>3/SP</td>
<td>0</td>
<td>0/0</td>
<td>20</td>
<td>128</td>
<td>31</td>
<td></td>
<td>Incomplete recovery/stable</td>
</tr>
<tr>
<td>4/RR(^b)</td>
<td>0</td>
<td>0/0</td>
<td>22</td>
<td>93</td>
<td>0</td>
<td></td>
<td>Incomplete recovery/progression(^2)</td>
</tr>
<tr>
<td>5/RR</td>
<td>1</td>
<td>0/0</td>
<td>17</td>
<td>75</td>
<td>0</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>6/RR</td>
<td>ND</td>
<td>ND</td>
<td>13</td>
<td>56</td>
<td>0</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>7/RR</td>
<td>1</td>
<td>0/0</td>
<td>12</td>
<td>74</td>
<td>4</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>8/RR(^c)</td>
<td>4</td>
<td>2/0</td>
<td>19</td>
<td>92</td>
<td>1</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>9/RR</td>
<td>0</td>
<td>0/0</td>
<td>13</td>
<td>104</td>
<td>3</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>10/RR(^d)</td>
<td>0</td>
<td>0/0</td>
<td>15</td>
<td>86</td>
<td>7</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>11/RR</td>
<td>0</td>
<td>ND</td>
<td>12</td>
<td>101</td>
<td>5</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>12/RR</td>
<td>6</td>
<td>0/0</td>
<td>12</td>
<td>64</td>
<td>12(^f)</td>
<td></td>
<td>Recovered/stable</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2 (2.8)</td>
<td>15.3 (3.6)</td>
<td>98.6 (35.8)</td>
<td>9.5 (12.4)</td>
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Abbreviations: CSF, cerebrospinal fluid; Gd+, gadolinium-enhancing; MS, multiple sclerosis; ND, not done; RR, relapsing-remitting; SP, secondary progressive; WBC, white blood cell.

\(^a\)Patient experienced a severe relapse with loss of independent functioning 1 month after restarting natalizumab therapy. At the time of relapse, a second magnetic resonance imaging scan when the patient was bedridden showed 37 Gd+ lesions.

\(^b\)Patients 4 and 10 experienced mild spinal cord relapses 13 months after starting natalizumab therapy and recovered. All other patients were relapse and progression free during natalizumab therapy.

\(^c\)Discontinued natalizumab therapy a year after restarting therapy because of progressive disease course.

\(^d\)Discontinued natalizumab therapy after only 1 more treatment and lost to follow-up 6 months later.

\(^e\)Patient was not compliant with natalizumab infusion regimen at onset of therapy but was compliant for 13 consecutive infusions prior to therapy interruption.

\(^f\)Magnetic resonance imaging obtained 4 months after last dose of natalizumab, not at the time of relapse onset.

Younger with a shorter duration of natalizumab therapy prior to therapy interruption, although this was a modest finding. Importantly, the degree of inflammatory response (ie, gadolinium-enhancing lesion number) post–therapy interruption in those experiencing a relapse was correlated with the degree of inflammation prior to initiation of therapy and seemed to increase with duration of therapy interruption. This has important implications for the monitoring of patients during natalizumab therapy interruption. The inflammatory response was most notable in certain patients with SPMS, in whom we observed a large number of small to medium gadolinium-enhancing lesions distributed throughout almost all areas of involved brain and par-

Figure. Gadolinium-enhancing, T1-weighted cranial magnetic resonance imaging in patient 1 after natalizumab therapy interruption, with widespread punctuate enhancement particularly noticeable along the edge of regions of encephalomalacia, which were present on older magnetic resonance imaging prior to the development of immune reconstitution inflammatory syndrome.
particularly noticeable along the edges of previous confluent T2 lesions and T1 black holes. Although we classified these individuals as having SPMS, those who experienced post–natalizumab therapy relapses were patients with moderately severe MS (significant disability for duration of disease, large T2 lesion burdens, and significant whole-brain atrophy) with a combination of progression, relapses, and gadolinium-enhancing lesions in the 2 years prior to natalizumab treatment. In 1 patient with SPMS (patient 1), a return of MRI activity 100 days following natalizumab therapy interruption continued to progress despite reinitiation of natalizumab therapy, culminating in a severe relapse with widespread inflammatory activity within 1 month of therapy restart. We believe it is unlikely that this relapse would have occurred without therapy interruption. First, this patient experienced complete cessation of all MS disease activity for 1.5 years prior to therapy interruption, despite significant evidence of disease activity prior to initiating natalizumab therapy (3 relapses in prior 2 years and 8 gadolinium-enhancing lesions at baseline). Second, there was no evidence of antinatalizumab antibodies on multiple evaluations prior to interruption of therapy or following the restart of therapy. Third, the return of disease activity on MRI that began during the interruption in therapy was associated with subtle evidence of clinical worsening by patient report that continued during the month following her therapy restart. She did not receive high-dose corticosteroid therapy until she was admitted to the hospital 1 month after therapy restart. A previous study reported that a single infusion of natalizumab did not enhance recovery from MS relapses and did not significantly decrease the number of gadolinium-enhancing lesions over 3 weeks compared with placebo, although there was a trend favoring a more rapid decrease in gadolinium-enhancing lesion number in the natalizumab treatment group. Another study reported 3 cases of severe relapse after the first infusion of natalizumab in patients with active RRMS. These authors suggested that an alteration of central nervous system regulatory networks by natalizumab therapy in this setting may worsen disease activity initially in some patients. This study as well as anecdotal experience suggest that a single dose of natalizumab monotherapy may not be effective at preventing continued progression of MS relapses, at least in some cases, and should be preceded by high-dose corticosteroid therapy to control the central nervous system inflammatory response prior to initiation of natalizumab therapy.

Our findings suggest that younger patients with more extensive disease and greater inflammatory activity before natalizumab treatment are at greatest risk for significant relapses after natalizumab therapy. The widespread inflammatory response observed in some of our cases is radiologically similar to the IRIS observed in cases of human immunodeficiency virus–associated PML once normal central nervous system immune function and surveillance is restored. As with PML–associated IRIS, some of our patients exhibited widespread gadolinium enhancement along the edge of numerous previously involved areas of demyelination by T2- and T1-weighted imaging (Figure). Immune reconstitution inflammatory syndrome is associated with a rapid reduction in human immunodeficiency virus 1 viral load and a simultaneous rapid rise in CD4+ T-lymphocyte counts after institution of highly active antiretroviral therapy. This is thought to create an enhanced immune response to disease-specific antigens, leading to an overproduction of inflammatory mediators in the context of previous immunosuppression. While classically associated with enhanced inflammatory responses to infectious processes, IRIS has also been associated with noninfectious immune-mediated conditions including systemic lupus erythematosus and autoimmune thyroid disorders. A similar mechanism directed against normal myelin antigens is likely at play in some of our cases. Natalizumab therapy is associated with a reduction in cerebrospinal fluid CD4 and CD8 T lymphocytes, CD19 B cells, and CD138 plasma cells and a reduction in the cerebrospinal fluid CD4:CD8 ratio. The same authors reported a clinical MS relapse in the patient with the highest total cerebrospinal fluid CD4 and CD8 T-cell count after cessation of natalizumab therapy, suggesting that a more rapid return of immune surveillance and function may be associated with IRIS in patients with MS. The suggestion from our study that this inflammatory response may become more widespread in certain patients with a longer duration of therapy interruption argues for careful monitoring during any planned natalizumab therapy interruption to detect the earliest signs of IRIS. Future studies must determine the relationship between this IRIS, immunoregulatory function, and cell trafficking during and after cessation of natalizumab therapy. For now, clinicians should be aware of this phenomenon and consider strategies to minimize the risk of IRIS after natalizumab discontinuation.
REFERENCES


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