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Preventing New Enhancing Lesions and Relapses After Discontinuing Tysabri®

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ABSTRACT

Introduction: Patients with multiple sclerosis (MS) receiving natalizumab (Tysabri®) infusions may discontinue treatment due to a positive JC virus (JCV) antibody status alone or positive status and length of time on infusions, as these factors increase the risk of developing progressive multifocal leukoencephalopathy (PML). Patients may experience a clinical relapse and/or develop new enhancing lesions following discontinuation of natalizumab, even in the absence of PML. For example, a patient in our practice experienced a clinical relapse with vertigo, optic neuritis, and weakness associated with 5 new enhancing brain lesions and 1 enhancing thoracic cord lesion. Therefore, we aimed to establish a treatment algorithm to reduce the risk of developing a relapse or new enhancing lesions after discontinuing natalizumab. Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel, repository corticotropin injection) is FDA-approved for treatment of acute MS exacerbations in adults.

Objective: The goal of our pilot case series was to use ACTH to reduce inflammation after discontinuing natalizumab and before symptoms or new enhancing MS lesions occurred (an off-label use).

Methods: Patients who discontinued natalizumab due to JCV antibody positive status (alone or in combination with length of time on infusion) were treated with ACTH gel 80 units SQ QD x 5 days at Week 4, Month 2, and Month 3 after discontinuing natalizumab. Disease-modifying therapy (DMT) was initiated at Week 4 with glatiramer acetate (Copaxone®) or Week 6 with intravenous immunoglobulin (IVIG). Data collected included information from patient records, MRIs, and neurological exam.

Results: We report results for 5 patients (4 female, 1 male; aged 35-57 years) who have been treated with the ACTH protocol following discontinuation of natalizumab treatment (duration of 8-31 months); 4 patients also received glatiramer acetate and 1 received IVIG. At varying intervals for MRI surveillance (2 patients at 4 months; 1 patient each at 6, 7, and 12 months), patients did not develop symptoms of a clinical MS relapse or develop new enhancing lesions on MRI using a 3 Tesla magnet with gadolinium.

Conclusions: Patients who were treated using a protocol of monthly pulse ACTH and a DMT following discontinuation of natalizumab showed no increase in new enhancing T2 lesions on MRI and no new clinical relapse symptoms during up to 12 months of follow up.

INTRODUCTION

- Patients with multiple sclerosis (MS) who are treated with natalizumab (Tysabri®) may be at risk for developing progressive multifocal leukoencephalopathy (PML).[1]
  - As of April 2, 2013, a total of 347 confirmed cases of PML associated with natalizumab have been reported.[2]
  - The risk for PML increases with positive JC virus (JCV) antibody status, prior immunosuppressant therapy, and increased duration of natalizumab therapy.[1]
- To reduce the risk for PML, clinicians or patients may choose to discontinue natalizumab treatment;[3] this decision may be based on a patient's JCV antibody status or length of time on infusions, alone or in combination.
- Some patients who discontinue natalizumab experience increased disease activity (ie, new enhancing lesions) and/or clinical relapses,[3-5] which may be severe.[6]
  - For example, after discontinuing natalizumab a patient in our practice experienced a clinical relapse with vertigo, optic neuritis, and weakness associated with 5 new enhancing brain lesions and 1 enhancing thoracic cord lesion. She was hospitalized and tested for PML (by lumbar puncture), which was negative for JCV antibody in cerebrospinal fluid. This patient was treated with high-dose intravenous methylprednisolone while hospitalized until return to baseline.
- Currently, no widely accepted evidence-based treatment algorithm exists to reduce or prevent the risk of developing a relapse or new enhancing lesions after discontinuing natalizumab infusions.
  - Approaches that have been reported—with varying success—include glatiramer acetate,[7,8] fingolimod,[9-11] pulse corticosteroids,[12] and pulse corticosteroids followed by glatiramer acetate.[13]
- Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel, repository corticotropin injection) is FDA-approved for the treatment of acute MS exacerbations in adults.[14]
  - ACTH exerts anti-inflammatory effects not only by stimulating endogenous corticosteroid production, but also through steroid-independent mechanisms mediated via melanocortin receptors.[15]
- Our practice has initiated a treatment protocol using ACTH gel that is intended to decrease or prevent a relapse or new enhancing lesions from developing after discontinuing natalizumab (ie, an off-label use). The rationale for this approach is that ACTH may reduce inflammation after discontinuing natalizumab and before symptoms or new enhancing MS lesions occur.
- This case series summarizes our initial experience with this protocol, based on 5 patients who were treated with ACTH gel after discontinuing natalizumab.

METHODS

- Patients were men or women with MS who discontinued natalizumab due to positive JCV antibody status alone (voluntary patient withdrawal) or positive JCV antibody status in combination with length of time on infusion (increased risk of developing PML).
- Patients were treated with ACTH gel 80 units SQ QD × 5 days at Week 4 after discontinuing natalizumab; this was repeated at Month 2 and Month 3.
- Disease-modifying therapy (DMT) was initiated either at Week 4 with glatiramer acetate (Copaxone®) or at Week 6 with intravenous immunoglobulin (IVIG).
- Data collected included information from patient records, magnetic resonance imaging (MRI; using a 3 Tesla magnet with gadolinium), and neurological exam.

RESULTS

- We report results for 5 patients (4 female, 1 male) aged 35–57 years (**Table 1**).
  - All patients had relapsing MS, with duration of disease ranging from 3 years to 13 years.

Table 1. Demographic Information

Patient	Age	Sex	Race	Type of MS	Duration of disease, y	Presenting symptoms
1	44	Female	Caucasian	RRMS	6	Optic neuritis, trigeminal neuralgia
2	37	Female	Caucasian	RRMS	3	Optic neuritis
3	35	Female	African American	RRMS	5	Optic neuritis, dizziness, left leg weakness
4	57	Female	Caucasian	RRMS	8	LLE weakness, parasthesias BLE
5	45	Male	Caucasian	RRMS	13	Optic neuritis, neurogenic bladder, spasticity

BLE, both lower extremities; LLE, lower left extremity; RRMS, relapsing remitting multiple sclerosis; MS, multiple sclerosis

- **Table 2** summarizes patient clinical data.
  - Prior DMTs included interferon beta-1a (Rebif®, 5 patients; Avonex®, 1 patient) and glatiramer acetate (Copaxone®, 2 patients).
  - All patients were treated with natalizumab 300 mg once per month; the duration of natalizumab treatment before discontinuation was 8–31 months.
  - All patients discontinued natalizumab treatment due to positive JCV antibody status and patient concerns about developing PML; 1 patient (patient #5) also discontinued due to increased time on natalizumab.

Table 2. MS Clinical and Treatment History

Patient	DMT(s) before natalizumab	Relapses on prior DMT(s)	AEs with prior DMT(s)	Natalizumab Treatment		Relapses on natalizumab	AEs on natalizumab	JC Virus (+/-)	PML (+/-)
				Duration, mo	Dosage (per mo)				
1	IFN, GA	2	Injection-site reactions, flu-like symptoms	8	300 mg	0	None	+	-
2	IFN	2	Spasticity, fatigue	14	300 mg	0	None	+	-
3	IFN	1	Leukopenia, diplopia	9	300 mg	0	None	+	-
4	IFN	3	LFT elevations	24	300 mg	0	None	+	-
5	IFN*, GA	4	Headache, injection-site reactions	31	300 mg	0	None	+	-

AEs, adverse events; DMT, disease-modifying therapy; GA, glatiramer acetate; IFN, interferon beta-1a; LFT, liver function tests; PML, progressive multifocal leukoencephalopathy. *Patient had been treated with Rebif® and Avonex®

- **Table 3** summarizes patient outcomes after discontinuing natalizumab.
  - All patients received the ACTH gel treatment protocol for 3 months.
  - Four patients also received glatiramer acetate and 1 received IVIG.
    - The patient who received IVIG had previously tried 3 other DMTs and did not want to resume treatment with an injectable medication.

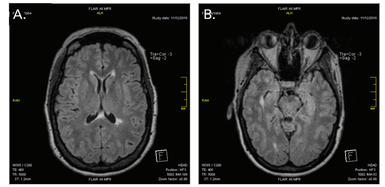
Table 3. Post-Natalizumab Treatments and Outcomes

Patient	ACTH duration, mo	ACTH dose (QD × 5 d/mo)	DMT	Follow-up time, mo	New MRI lesions	Clinical relapses post-natalizumab
1	3	80 units	GA	12	None	None
2	3	80 units	GA	7	None	None
3	3	80 units	GA	6	None	None
4	3	80 units	GA	4	None	None
5	3	80 units	IVIG	4	None	None

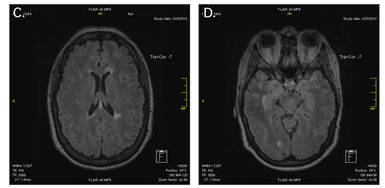
ACTH, adrenocorticotropic hormone; DMT, disease-modifying therapy; GA, glatiramer acetate; IVIG, intravenous immunoglobulin; QD, once daily

  - At varying intervals for MRI surveillance (from 4 months to 12 months):
    - No patients developed symptoms of a clinical MS relapse.
    - No patients developed new enhancing lesions on MRI.
    - MRI images from scans performed before and after natalizumab discontinuation are shown for patient #3 (**Figure 1**) and patient #4 (**Figure 2**).

Figure 1. MRI shows no new enhancing lesions following ACTH gel treatment after discontinuation of natalizumab (Patient #3)

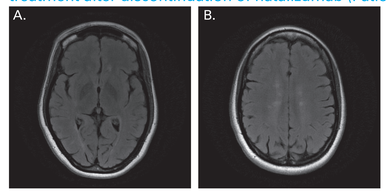


A-B. Before starting natalizumab treatment (approximately 6 months before natalizumab treatment was started)

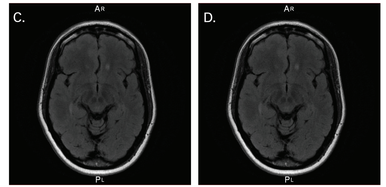


C-D. After 3 months of ACTH gel treatment (about 6 months after discontinuation of natalizumab)

Figure 2. MRI shows no new enhancing lesions following ACTH gel treatment after discontinuation of natalizumab (Patient #4)



A-B. During natalizumab treatment (about 1 month before discontinuation of natalizumab)



C-D. After 3 months of ACTH gel treatment (about 6 months after discontinuation of natalizumab)

CONCLUSIONS

- Patients who were treated using a protocol of monthly pulse ACTH gel and a DMT after discontinuing natalizumab showed no increase in new enhancing T2 lesions on MRI and no new clinical relapse symptoms during up to 12 months of follow-up.
- Further research is needed to evaluate the efficacy of ACTH gel for preventing or reducing the risk of clinical relapses or new lesions in patients who discontinue natalizumab treatment.

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