

# Central Nervous System Herpes Simplex and Varicella Zoster Virus Infections in Natalizumab-Treated Patients

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**We report on 20 natalizumab-treated patients with multiple sclerosis who developed laboratory-confirmed central nervous system (CNS) herpesvirus infections. In addition to progressive multifocal leukoencephalopathy, other CNS opportunistic infections have been rarely reported during natalizumab treatment. We encourage heightened awareness due to the risk for serious outcomes.**

**Keywords.** HSV; VZV; encephalitis; meningitis; natalizumab.

Natalizumab (NTZ, Tysabri), a recombinant humanized monoclonal antibody used to treat multiple sclerosis (MS) and Crohn's disease, binds to the  $\alpha 4$  subunit of  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  integrins, which are expressed on all leukocytes except neutrophils, and interferes with their attachment to adhesion molecules on endothelial cells. As a result, NTZ hinders inflammatory cell migration into the central nervous system (CNS) and the gastrointestinal tract, providing clinical benefit by relieving symptoms and attenuating the risk for disabling relapses [1, 2].

NTZ has differential effects on T-lymphocyte counts in the CNS compared with the peripheral blood of MS patients. NTZ substantially decreases the CD4(+)/CD8(+) ratio in the cerebrospinal fluid (CSF) compared with the peripheral blood, resulting in impaired immune surveillance [3, 4]. Cases of progressive multifocal leukoencephalopathy (PML), a serious opportunistic

infection of the brain due to the John Cunningham polyomavirus [5, 6], provide evidence of this adverse effect.

Herpes simplex virus (HSV) and varicella zoster virus (VZV) can cause CNS infections through various pathologic mechanisms. CNS infections can range from asymptomatic meningeal seeding to fulminant life-threatening encephalitis. Reactivation of latent virus within the brain is also possible. HSV-1 can spread from peripheral ganglia, such as the trigeminal ganglion, to the temporal lobes of the brain to cause encephalitis [7, 8].

We describe the potential association of NTZ treatment with CNS herpesvirus infections in 20 MS patients. To our knowledge, this is the largest case series in the English language medical literature.

## METHODS

We searched the US Food and Drug Administration's (FDA's) Adverse Event Reporting System (FAERS) for postmarket reports of CNS herpesvirus infections in NTZ-treated MS patients between November 2004 and December 2012 using the following Medical Dictionary for Regulatory Activities (MedDRA) terms [9]: herpes zoster infection neurological, meningitis herpes, meningitis viral, meningoencephalitis herpetic, varicella encephalitis, encephalitis herpes, encephalitis viral. We also searched MEDLINE for relevant English language articles. We limited our analyses to reports of CNS herpesvirus infections that presented during or following recent exposure to NTZ in which laboratory methodologies for viral detection were described.

FAERS is a computerized repository of spontaneous postmarket adverse event reports submitted by product manufacturers, consumers, and healthcare professionals. FAERS supports the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products.

In this case series, we provide only a descriptive analysis using measures of central tendency owing to missing data and the lack of a concurrent comparator treatment group. FAERS data cannot be used to estimate incidence.

We conducted exploratory analyses to assess the occurrence of other CNS opportunistic infections in NTZ-treated patients and to assess CNS herpesviruses infections in MS patients not given NTZ. Methodologically, we searched FAERS for postmarket reports received between 2004 and 2012 of laboratory-confirmed CNS infections involving pathogens other than herpesviruses in NTZ-treated patients. We also searched reports of laboratory-confirmed CNS herpesvirus infections in MS patients treated with other therapies.

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## RESULTS

Between 2004 and 2012, FDA received postmarket reports for 20 unique patients with CNS herpesvirus infections during or following recent NTZ treatment (see Table 1). All infections were laboratory confirmed by polymerase chain reaction of the CSF for HSV or VZV. Six cases were also reported in the literature. The median age for all patients was 44 years (range, 30–63 years). Sixteen patients were female (80%), which likely reflects the higher frequency of MS in women [10]. Patients received a median of 21 monthly doses of NTZ prior to presentation. Of the 20 patients, 7 received prior immunosuppressives (IS), 7 did not receive IS, and data were missing for the remaining 6 patients. Past medical history was infrequently described.

The 20 patients in our series included the following pathogens and clinical syndromes: 5 HSV-1 encephalitis cases, 5 HSV-2 cases (2 encephalitis, 2 meningitis, and 1 meningoencephalitis), 6 HSV nontyped as to HSV-1 or -2 (3 encephalitis and 3 meningitis), and 4 VZV infections (2 meningitis, 1 meningoradiculitis, and 1 meningomyelitis). The HSV encephalitis cases usually presented with seizures, altered mental status, and fever. HSV and VZV meningitis frequently presented with headache, photophobia, fever, and nuchal rigidity. Two VZV patients exhibited CNS manifestations without reported rash; this clinical presentation could be a diagnostic dilemma for clinicians [11, 12].

Eighteen patients received systemic antiviral therapy (17 acyclovir-treated and 1 valacyclovir-treated). Antiviral therapy was not reported for 2 cases. Nineteen patients (95%) were hospitalized, including 5 (25%) admitted to an ICU. Median hospitalization length was 15 days (range, 0–40 days). While hospitalized, 1 patient each experienced pneumonia and esophagitis and 3 patients suffered renal insufficiency secondary to acyclovir administration.

Two patients died from their infections; postinfectious complications included meningitis relapse ( $n = 2$ ) and VZV retinitis ( $n = 1$ ). Most surviving patients recovered as of the latest follow-up assessment; however, 4 patients had persisting neurologic or neuropsychiatric sequelae. One patient developed laboratory-confirmed PML following successful treatment of HSV-2 meningoencephalitis.

Our exploratory analyses yielded individual postmarket reports of NTZ-treated MS patients with cerebral toxoplasmosis (patient with underlying lung cancer), CNS cytomegalovirus, and cryptococcal meningitis (previously received mitoxantrone). We also retrieved 2 reports of laboratory-confirmed CNS herpesvirus infections in patients receiving other MS regimens: 1 fingolimod-treated patient with cutaneous zoster complicated by VZV encephalitis [13] who previously received NTZ and 1 mitoxantrone-treated patient with zoster and VZV meningitis who received prednisolone.

## DISCUSSION

The substantial decline in CD4 T cells in the CNS induced by NTZ impairs immune surveillance, which increases the risk for opportunistic infections. Although NTZ-associated PML has been frequently described, other CNS infections have rarely been reported. Controlled clinical trials of NTZ in MS patients did not reveal a propensity for serious infections compared with controls. Controlled studies of Crohn's disease demonstrated opportunistic infections in <1% of NTZ recipients; however, some received concomitant IS. In postmarketing, few CNS HSV and VZV infections have been reported [14].

HSV is the most common cause of sporadic fatal encephalitis cases in the United States, with an incidence estimated at 1:250 000 to 1:500 000 individuals per year [15]. HSV-1 accounts for >90% of the cases [16]. Through February 2012, 99 571 patients received NTZ [6]. Of the 8 HSV encephalitis cases (excluding HSV-2) in our case series, 7 were reported prior to that date. Thus, notwithstanding the limitations in case ascertainment with FAERS and NTZ exposure data, the number of HSV encephalitis patients in our case series appears overrepresented compared with the expected background rate.

Animal models of ocular herpes demonstrate that CD8(+) T cells have a critical protective role within the brain in preventing potentially fatal CNS infection [17]. In an experimental mouse model of herpes encephalitis, the early immunologic response to CNS herpes infection involved the influx of macrophages and neutrophils, whereas a subsequent influx of CD8 (+) T cells (predominantly) constituted the ongoing immune response to such infection in the brain [18]. CD8 T cells may also be important in recovery from HSV-1 infection; in a mouse model, HSV-specific CD8 T cells appear to limit viral spread in the brain if sufficient numbers are present early in infection [19]. Although NTZ enhances the risk for serious CNS herpesvirus infections by impairing immune surveillance through CD4 T-cell depletion, hypothetically the product may also weaken protective immune defenses by impairing CD8 T-cell migration into the CNS.

Compared with other MS treatment regimens evaluated in our exploratory analyses, the postmarketing data from FAERS suggest that NTZ may confer a predilection for CNS herpesvirus infections. Two NTZ-treated adults developed HSV-2 encephalitis, an unusual finding considering that HSV-2 is more frequently associated with neonatal encephalitis. No FAERS reports of HSV-2 CNS infections were retrieved for adults receiving other MS drug therapies. We also retrieved only 2 reports of laboratory-confirmed VZV and no cases of HSV (HSV-1 or HSV-nontyped) CNS infections in patients receiving other MS regimens compared with 15 cases among NTZ-treated patients. However, further assessment was limited; in contrast to NTZ, which has been marketed continuously since 2006,

**Table 1. Postmarket Cases of Laboratory-Confirmed Central Nervous System Herpesvirus Infections in Natalizumab-Treated Multiple Sclerosis Patients**

Case No.	FDA Received Year	Age (y)/Gender	Country	Pathogen	Clinical Syndrome	NTZ Monthly Doses	Prior IS	Primary Antiviral Treatment	Hospitalization (d)	Complications	Clinical Outcome at Last Follow-up
1	2005	51/female	United States	HSV <sup>a</sup>	M	1	None	ACY, FAM	7	Recurrent meningitis	Recovered
2 [20]	2008	44/female	Germany	HSV <sup>a</sup>	E	6	MTX, MEX	ACY	35 <sup>b</sup>	Pneumonia	Recovered
3	2011	34/female	Great Britain	HSV <sup>a</sup>	E	40	None	ACY	30	None reported	Recovered
4	2012	34/female	United States	HSV <sup>a</sup>	M	22	NR	ACY	10	None reported	Recovered
5	2012	38/male	Spain	HSV <sup>a</sup>	M	7	NR	ACY	6	None reported	Not recovered
6	2012	43/female	Germany	HSV <sup>a</sup>	E	55	NR	NR	21	None reported	Recovered
7	2009	50/female	United States	HSV1	E	34	None	ACY	21 <sup>b</sup>	None reported	Neurological deficit
8	2009	30/female	France	HSV1	E	23	MTX	ACY	21 <sup>b</sup>	None reported	Recovered
9	2010	48/female	United States	HSV1	E	21	MTX	ACY	NR <sup>b</sup>	None reported	Death
10 [21]	2011	36/female	France	HSV1	E	6	MMF	ACY	40	Renal insufficiency due to ACY	Neurological deficit
11	2011	60/female	United States	HSV1	E	47	NR	ACY	17 <sup>b</sup>	Renal insufficiency due to ACY	Neurological deficit
12	2005	54/male	United States	HSV2	E	1	MTX, MEX	ACY	10	None reported	Death
13 [22]	2009	50/female	United States	HSV2	M	14	None	ACY, VACY	7	Postviral encephalopathy; recurrent meningitis	Neurological deficit
14	2010	63/female	United States	HSV2	E	24	NR	NR	NR	None reported	NR
15 [23]	2011	40/male	Switzerland	HSV2	ME	28	MTX, AZA	VACY	0	None reported	Recovered
16	2011	36/female	United States	HSV2	M	28	NR	ACY	3	None reported	Recovered
17 [24]	2008	51/male	United States	VZV	M	20	None	ACY, VACY	7	VZV retinitis; renal insufficiency due to ACY	Recovered
18	2008	37/female	France	VZV	MR	7	AZA, MTX	ACY	21	Esophagitis	Recovered
19	2012	62/female	Netherlands	VZV	M	23	None	ACY	NR	None reported	Recovered
20 [25]	2012	32/female	France	VZV	MM	5	None	ACY	15	None reported	Recovering

Abbreviations: ACY, intravenous acyclovir; AZA, azathioprine; E, encephalitis; FAM, famciclovir; FDA, US Food and Drug Administration; HSV, herpes simplex virus; IS, prior treatment with immunosuppressive therapies; M, meningitis; ME, meningoencephalitis; MEX, methotrexate; MM, meningomyelitis; MMF, mycophenolate mofetil; MR, meningoradiculitis; MTX, mitoxantrone; NR, not reported; NTZ, natalizumab; VACY, valacyclovir; VZV, varicella zoster virus.

<sup>a</sup> HSV not typed as to HSV-1 or HSV-2.

<sup>b</sup> Hospitalization included stay in intensive care unit.

fingolimod has only been marketed in the United States since 2010. Consequently, the time period for accrual of postmarket safety reports for fingolimod was not comparable to NTZ. Evaluation of other opportunistic CNS infections in NTZ-treated patients was limited by their infrequent occurrence and by confounding from prior immunosuppressive therapies and underlying medical conditions.

In our case series, many patients experienced improvement or resolution of their infections after NTZ withdrawal and initiation of acyclovir. It is uncertain whether adjunctive measures (such as plasma exchange) to remove NTZ from peripheral circulation could reconstitute immune surveillance and alter the course or prognosis of these infections. Additionally, the potential role for prophylactic oral antivirals in preventing relapses remains to be elucidated. Notwithstanding treatment interventions, however, adverse outcomes and fatalities were observed.

In summary, our case series illustrates that HSV and VZV cause serious and potentially life-threatening opportunistic infections of the brain in NTZ-treated MS patients. Although a temporal association was evident between exposure to the biologic product and the CNS infections buttressed by the preclinical data, causality assessments were limited by missing data and channeling bias. Missing data precluded us from assessing the potential role of prior immunosuppressive therapies in enhancing the risk for CNS infections in this case series. Clinicians need heightened awareness of these infections in view of the risks for serious outcomes, including prolonged hospitalizations, persisting neuropsychiatric sequelae, and death.

## Notes

**Disclaimer.** The findings and conclusions expressed in this report are those of the authors and do not necessarily represent the views of the US Food and Drug Administration.

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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