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LETTER TO THE EDITOR

Report of Three Cases of Herpes Zoster During Treatment with Natalizumab

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While there is no doubt that natalizumab is a very effective treatment for multiple sclerosis (MS) [1], the worries about the safety of this drug continue. Natalizumab (Tysabri®; Biogen Idec, Cambridge, MA, USA, and Elan Pharmaceuticals, Dublin, Ireland) was the first FDA-approved monoclonal antibody for the treatment of MS. Natalizumab is a humanized monoclonal IgG4κ antibody that selectively binds to the α4-integrin (subunit of the leukocyte adhesion molecules $\alpha4\beta1$ and $\alpha4\beta7$) component of adhesion molecules found on lymphocytes, monocytes, and eosinophils. Natalizumab inhibits the interaction of $\alpha4\beta1$ with VCAM-1 and of $\alpha4\beta7$ with MAdCAM-1. VCAM-1 and MAdCAM-1 are found on endothelial cells and interact with $\alpha4\beta1$ and $\alpha4\beta7$ on leukocytes for firm adherence of leukocytes to endothelial cells, which is a requisite step for their extravasation into inflamed tissue [2].

The main concern regarding the association of natalizumab and opportunistic infections is in relation to progressive multifocal leukoencephalopathy (PML) [3] caused by the JC virus (JCV). Doctors prescribing natalizumab are well aware of this potential complication, and JCV testing is now frequently used by neurologists to establish the potential risks of prescribing natalizumab to a given patient. However, although extremely rare, other viral infections have been described in patients using natalizumab, particularly herpes simplex virus (HSV) meningitis [4] and encephalitis [5].

Varicella zoster virus (VZV) reactivation has not been described in patients using natalizumab, although it has been known to affect patients using fingolimod, which is another new drug for MS. In fact, YZV reactivation was found to be fatal in a patient receiving fingolimod [6], but only at unusually high doses [7].

To the best of our knowledge, there have been no case reports on the association of natalizumab and herpes zoster in patients with MS. The purpose of the present study was to report on three cases of herpes zoster manifestation in patients undergoing treatment with natalizumab.

Case 1 – Female, 62 years old with a 20-year history of MS, still presenting relapses of demyelination and therapeutic failure with first-line drugs for the treatment of MS (interferon beta and glatiramer acetate). Her neurological disability assessed using the expanded disability status scale (EDSS) [8] was 5.0, meaning that she had moderate difficulty in walking unaided. After the fourth monthly infusion of natalizumab, the patient developed herpes zoster in the cervical region and natalizumab was withdrawn and glatiramer acetate was restarted.

Case 2 – Female, 28 years old, presenting frequently relapses of demyelination of the central nervous system without response to first-line therapy for the treatment of MS. The degree of disability of this patient was 3.5 on the EDSS scale, meaning that she had mild difficulty in walking long distances. After the seventh monthly infusion, the patient presented severe intercostal herpes zoster, leading to discontinuation of the drug. The patient continued with monthly pulses of corticosteroid during the short follow-up, because she moved to another MS service.

Case 3 – Male, 54 years old, presenting therapeutic failure with first-line treatments of MS. Disability degree rated as 4.5 on the EDSS scale, meaning the patient had moderated difficulty to walk. After the 28th infusion, the patient presented intercostal herpes zoster. The patient continued on natalizumab.

The patients described above were receiving the medication at the appropriate dose and posology. They were treated with

acyclovir when herpes zoster was diagnosed. Except for MS, they were in good general health. The three cases reported here serve to increase the awareness of neural viral infections in patients with MS treated using natalizumab. Although, with great reason, much attention is given to the potential for JCV infection during the use of natalizumab, little is known or written about other viral infections.

The mechanism of action of VZV reactivation during the use of natalizumab can be debated, but immunosuppression of the nervous system must be at its core. VZV reactivation in immunosuppressed patients who received organ transplants [9] is well documented. There has been one report [10] of high titers of VZV in patients with MS in the week following natalizumab infusion. It is possible that VZV reactivation leading to herpes zoster in these three patients was nothing more than a fortuitous finding, but it is also possible that the clinical manifestation of VZV was related to immunosuppression of the nervous system. Further studies on this subject and more reported cases may add to the discussion and to the guidelines concerning herpes zoster manifestations in MS patients using natalizumab and other immunosuppressive drugs. In fact, the lack of guidelines is the reason the three cases presented here had different recommendations for the follow-up treatment.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Stephenson JJ, Kern DM, Agarwal SS, et al. Impact of natalizumab on patient-reported outcomes in multiple sclerosis: A longitudinal study. *Health Qual Life Outcomes* 2012;**10**:155.
2. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: The leukocyte adhesion cascade updated. *Nat Rev Immunol* 2007;**7**:678–689.
3. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012;**366**:1870–1880.
4. Shenoy ES, Mylonakis E, Hurtado RM, Venna N. Natalizumab and HSV meningitis. *J Neurovirol* 2011;**17**:288–290.
5. Kwiatkowski A, Gallois J, Bilbault N, Calais G, Mackowiak A, Hautecoeur P. Herpes encephalitis during natalizumab treatment in multiple sclerosis. *Mult Scler* 2012;**18**:909–911.
6. Cohen JA, Barkof F, Comi G, TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;**362**:402–415.
7. McDonagh M. *Drug class review: Disease-modifying drugs for multiple sclerosis: Single drug addendum: Fingolimod*: Final Original Report. Portland (OR): Oregon Health & Amp; Science University, 2011.
8. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* (Cleveland) 1983;**33**:1444–1452.
9. Mustapic Z, Basic-Jukic N, Kes P, et al. Varicella zoster infection in renal transplant recipients: Prevalence, complications and outcome. *Kidney Blood Press Res*. 2011;**34**:382–386.
10. Scheiss N, Zong J, Hayward G, Calabresi P, et al. Reactivation of herpes virus in multiple sclerosis patients on natalizumab therapy [P03.163]. Poster presentation, April 29, 2009 at the American Academy of Neurology Congress.