Occurrence of Herpes Zoster in Multiple Sclerosis Patients Treated with Natalizumab

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BACKGROUND

Herpes zoster (HZ) is caused by reactivation of the varicella-zoster virus (VZV). Risk factors include immunocompromised status, immunosuppressive treatment and age-related waning of cell-mediated immunity. It is estimated that 2.2 to 4.8 per 1,000 persons per year develop zoster.

VZV primary infection leads to varicella or chicken pox, which typically occurs among children. More than 90% of the adult population has had varicella but no immunologic parameters have been identified to distinguish who will develop zoster.

Viral reactivation is thought to be a result of aging-related waning of cell-mediated immunity. It may occur decades after initial infection causing herpes zoster and requires the spread of the virus to neighboring neurons within the ganglia.

Acutely, the most significant clinical manifestation of herpes zoster is neuritis, with the later possibility of developing post-herpetic neuralgia. Immunocompromised patients and those with immunosuppressive treatment are considered to be at increased risk, but fatalities caused by viral dissemination in this group of patients are rare.

Multiple sclerosis is an immune-mediated disorder that occurs in susceptible individuals. The passage of autoreactive inflammatory cells through the blood brain barrier leads to CNS demyelination. Natalizumab is a monoclonal antibody that blocks the binding of activated T-cells to the endothelial receptors, diminishing cell trafficking and disease activity.

The number of CD4+ and CD8+ T lymphocytes, CD19 and CD 138+ plasma cells in the CSF were found to be decreased in patients with MS on natalizumab therapy and remained decreased six months after therapy cessation. The CSF CD4/CD8 ratios from MS natalizumab treated patients were similar to those observed in HIV-infected controls.

The prevalence of zoster among MS patients has not been described to differ from that of normal individuals. It seems that glatiramer acetate and interferon immunomodulatory treatment has no impact on HZ incidence.

OBJECTIVES

To determine the occurrence of herpes zoster among MS patients treated with natalizumab.

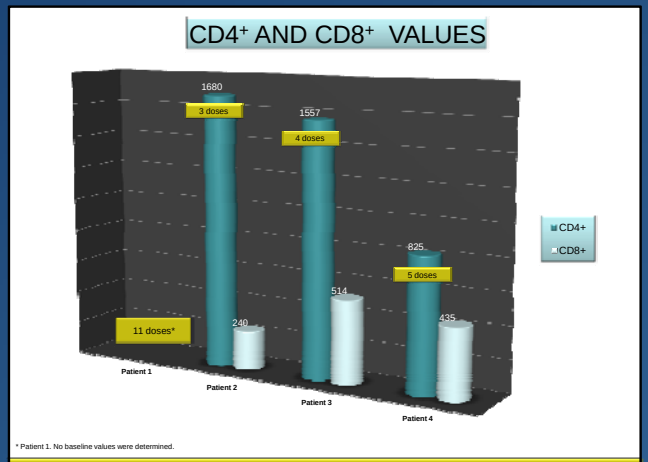
METHODS

Review of medical records of MS patients on nataluzimab in our center .

RESULTS

CASE 1. A 34 year old woman with RRMS diagnosed in 2006. Prior to natalizumab, therapy included interferon beta 1a IM and glatiramer acetate. After 11 doses of natalizumab she developed herpes zoster on the left T6-T9 level. Natalizumab was withheld for 3 months and 1 gram of valacyclovir daily was prescribed as long term prophylaxis therapy. She developed post-herpetic neuralgia.

CASE 2. A 43 year old woman diagnosed with RRMS in 1991. Prior to natalizumab she was treated with interferon beta 1b. She developed herpes zoster after the 3rd dose of natalizumab and was placed on long term prophylaxis with 1gram of valacyclovir daily. The peripheral blood baseline $CD4^+$ count was 1680/cumm and $CD8^+$ count was 240/cumm. No history of exposure was mentioned.



Peripheral $CD4^+$ and $CD8^+$ absolute counts prior to natalizumab.

CASE 3. A 43 year old woman diagnosed with RRMS in 1994. Prior therapy included interferon beta 1a IM, glatiramer acetate and interferon beta 1a SC. Her peripheral absolute $CD4^+$ count was 1557/cumm and $CD8^+$ 514/cumm at baseline. She was diagnosed by her general physician with herpes zoster after her 5th natalizumab infusion. No complications were reported.

CASE 4. A 56 year old woman diagnosed with RRMS in 1982. Prior to natalizumab, treatment included interferon beta 1a IM, glatiramer acetate and interferon beta 1b. Natalizumab was instituted in August 2008. Following the 4th infusion, she developed herpes zoster at the T4-5 level. She had prior history of herpes zoster in 1986 without residual symptoms. She was diagnosed with rheumatoid arthritis in late 2008.

Of 120 MS patients receiving natalizumab, four experienced an episode of HZ. All the patients received antiviral treatment.

All the patients were women with RRMS with a median age of 43. They were previously treated with interferon beta and three of them had also used glatiramer acetate.

At the time of HZ, the patients had received 3, 4, 5 and 11 doses of monotherapy. One patient had experienced a remote episode of HZ and was recently diagnosed with RA. One of the patients developed post-herpetic neuralgia. No severe complications developed.

CONCLUSIONS

The occurrence of HZ among natalizumab treated MS patients in our center was higher than that of the general population.

Various observations can be made from our patients' demographics; unfortunately our small sample size limits the power of such. There did not seem to be a trend for increased HZ incidence with an increasing number of natalizumab doses, previous disease modifying therapy or number of years since diagnosis.

The patients that developed HZ within the first 5 months of treatment were older when compared to the patient that developed it after the 11th dose. It is possible that age may be an independent risk factor toward development of HZ as occurs in the general population.

Peripheral baseline CD4 and CD8 values in our patients were no different from that of the general population; yet the patient with the lowest concentration of $CD8^+$ in peripheral blood developed HZ earlier in the course of treatment.

The distribution of lesions in two of our patients involved more than one dermatome. No serious complications were reported but one patient experienced post-herpetic neuralgia.

In natalizumab clinical trials a small excess of herpes infections was reported. The post-release monitoring disclosed one case of fatal herpesvirus encephalitis and one nonfatal case of herpesvirus meningitis while on therapy.

In view of a higher HZ incidence in MS patients treated with natalizumab and the serious complications reported, we consider long term antiviral prophylaxis appropriate after HZ diagnosis in patients continuing to receive natalizumab.

1. Arvin A. Varicella-Zoster Virus. Clin Mircrob Rev; 1996
2. Harpaz R, Ortega-Sanchez I, Seward J. Prevention of Herpes Zoster. Recommendations of the Advisory Committee on Immunization Practices. National Center for Immunization and Respiratory Diseases, CDC.
3. Cohen & Powderly: Infectious Diseases, 2nd ed.
4. Mandell, Bennett, & Dolin: Principles and Practice of Infectious Diseases, 6th.
5. Weinberg JM. Herpes zoster: Epidemiology, natural history, and common complications.
6. Winn,O, van Loon AM, Schuller M. Clinical Diagnosis of Herpes Zoster in Family Practice. Ann of Family Medicine.
7. Noseworthy J, Lucchinetti C, Rodriguez M. Multiple Sclerosis. NEJM 2000, 343:13 (938-950)
8. Stuve,O. The effects of natalizumab on the innate and adaptive immune system in the central nervous system. Jour Neuro Scie
9. Goodin D.S., Cohen B.A., O'connor, Stevens J.C., Assessment: The use of natalizumab for the treatment of multiple sclerosis. AAN
10. Ransohoff R. Natalizumab for Multiple Sclerosis. NEJM 2007,356: 2622-9