Persistence of Cerebrospinal Fluid Oligoclonal Bands after Natalizumab Treatment of Multiple Sclerosis Patients

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INTRODUCTION

Multiple Sclerosis (MS) is an inflammatory disorder characterized by destruction of myelin in the central nervous system (CNS). Pathologically, autoreactive T-cells of multiple subtypes have been identified in MS lesions. However, the humoral immune system has been increasingly implicated in MS pathophsyiology. Although there is no specific test for MS, intrathecal immunoglobulin production in an oligoclonal pattern is present in the cerebrospinal fluid (CSF) in a majority of patients. The role of these immunoglobulins is as of yet unknown and no pathological targets have been identified.

Previous research has indicated that multiple immune modifying treatments have not had an impact on the presence of oligoclonal bands (OCBs). These include Beta interferons, Rituximab, as well as immune ablation with cyclophosphamide followed by autologous bone marrow transplantation. Recently, however, Glehn et al (2012) published an article describing the disappearance of OCBs in four out of six relapsing-remitting multiple sclerosis (RRMS) patients treated with Natalizumab after a mean of ten infusions.
Natalizumab is a humanized monoclonal antibody which binds alpha-4 integrin, an important cell adhesion molecule. Blocking alpha-4 integrin presumably prevents peripheral immune cells from crossing the blood-brain barrier (BBB) and entering the CNS. Prior to the article by Glehn et al, the effect of Natalizumab on OCBs had not been examined.

METHODS

Included in this study were 14 patients (9 female) on Natalizumab for the treatment of RRMS, undergoing lumbar puncture (LP) for CSF monitoring for the John Cunningham Virus (JCV), which causes the CNS infection, progressive multifocal leukoencephalopathy (PML). The mean age of patients were 41.4 years (range 23 – 62). Mean disease duration at the time of second LP was 14.2 years (range 3 – 30). Results were compared to reports of OCB testing done previously, presumably at the time of presentation or diagnosis. The study was approved by the local institutional review board. All patients provided written informed consent.

CSF OCBs were analyzed by isoelectric focusing followed by immunoblotting in 11 clinically definite RRMS who tested positive for OCBs at baseline. All samples were analyzed by identical methods and all cases of OCBs in CSF were compared to serum to ensure intrathecal production. In addition, 3 patients who had negative CSF OCBs at baseline were re-examined post-treatment.

RESULTS

Mean duration of treatment with Natalizumab was 22.2 months (range 6 – 51). Following Natalizumab treatments, 9 out of 11 patients remained OCB positive. There were no differences between OCB positive and negative patients in terms of disease subtype, duration of disease, clinical or radiographic response to Natalizumab treatment, or disability scores. Among the 9 OCB positive patients, there were no significant differences in the number of OCBs detected in pre-treatment compared to post-treatment samples. Of the 3 OCB-negative patients at baseline, 1 developed detectable bands after 23 treatment cycles and 1 continued to have 1 band at 31 treatments.

	Bands Pre Tx	Bands Post Tx	# of Tx's
1	2	>5	6
2	2	0	20
3	4	>5	28
4	>5	>5	7
5	5	>5	9
6	>5	4	42
7	>5	>5	14
8	"positive"	>5	19
9	11	0	40
10	"positive"	>5	51
11	>12	>5	17
12	0	0	4
13	0	2	23
14	1	1	31

All patients were clinically stable on Natalizumab treatment at the time of the second LP. Additionally, brain MRI in 13 out of 14 patients around the time of 2nd LP confirmed no evidence of disease activity. (The remaining patient has not had subsequent MRI's.)

CONCLUSIONS

Our investigation found that in most patients, CSF oligoclonal banding is not affected by Natalizumab treatment. Our results do not support the previous assertion that Natalizumab treatment "converts" OCBs from positive to negative. A probable factor to explain this discrepancy in findings may include analysis of only 6 patients in the previous report. Our analysis is ongoing to include a larger sample of patients.

Dr. Stark has received personal compensation for activities with Biogen Idec. Mr. Koffler has nothing to disclose. Dr. Sadiq has nothing to disclose.