Natalizumab and rapidly evolving central nervous system lymphoma in VigiBase

D. Sartori1, C. Westerberg1, B. Grundmark1,2
1 Uppsala Monitoring Centre, Uppsala, Sweden; 2 Department of Surgery, Uppsala University, Uppsala, Sweden

Background
Natalizumab, an anti-α4β1 integrin inhibitor, limits lymphocyte passage through the blood-brain barrier. It is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) via monthly infusions. Central nervous system lymphoma (CNSL) is rare, with incidence increasing with age, particularly after age 55[1]. Risk factors include immunosuppression and EBV infection. MS and CNSL may overlap and biopsy is preferred for diagnosis, with imaging being less reliable[2]. A two-year natalizumab study showed no impact on incidence of malignancies[3]. Chronic immunosuppressive treatment can predispose patients to CNSL. Immunosuppressants such as azathioprine are labelled for this condition. No statistical association was found between multiple sclerosis and CNSL.

CNSL may be misdiagnosed as MS via imaging, making biopsy more reliable. Both conditions respond positively to high corticosteroid doses. However, corticosteroids may reduce the power of biopsy to tell MS from CNSL.

Central nervous system lymphoma (CNSL) is a rare cancer, most commonly of the diffuse large B-cell type, that mostly affects males. Risk factors include Epstein-Barr virus (EBV), profound immunosuppression (i.e. HIV/AIDS), age > 65.

Multiple sclerosis is a myelin-disrupting autoimmune disease, accompanied by loosening of the blood-brain barrier. Multiple sclerosis may lead to vision loss, fatigue and gait disturbances. It is managed with immunosurveillance promoted by natalizumab.

Natalizumab has been approved for use in severe relapsing remitting multiple sclerosis (RRMS) for patients that do not respond to adequate treatment, with one or more gadolinium enhancing lesions or whose lesions have worsened significantly in between two MRIs.

Aim
To assess the drug-adverse event combination (DEC) natalizumab with MedDRA Preferred Term "Central nervous system lymphoma" in VigiBase, alongside published literature cases.

Methods
Reports of the DEC until May 2015 were extracted from VigiBase. Literature cases were matched and duplicates removed. Clinical findings, co-reported terms and drugs, and duration of treatment were appraised.

Results
There were 12 cases whereof 5 from literature with an IC of 3.12 indicating the DEC natalizumab study showed no impact on incidence of malignancies[3]. Clinical findings, co-reported terms and drugs, and duration of treatment were appraised. Several VigiBase case reports present similarities with the well described literature cases, being EBV/HIV negative and presenting with rapid lymphoma progression. Reduced lymphocyte CNS surveillance, mediated by natalizumab mechanism of action, may accelerata pre-existing CNSL growth. Despite uncertainties regarding a causal role of natalizumab[6], we believe VigiBase data adds sufficient evidence to discuss an update to the natalizumab safety profile.

Footnote: as of 04-2017 an additional 13 cases, still under assessment by UMC, have been reported to VigiBase.

Conclusion
Several VigiBase case reports present similarities with the well described literature cases, being EBV/HIV negative and presenting with rapid lymphoma progression. Reduced lymphocyte CNS surveillance, mediated by natalizumab mechanism of action, may accelerate pre-existing CNSL growth. Despite uncertainties regarding a causal role of natalizumab[6], we believe VigiBase data adds sufficient evidence to discuss an update to the natalizumab safety profile.

References

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VigiBase case series was similar to literature cases, with respect to time to diagnosis, patients’ immunocompetence and relatively young age, with lesions described as rapidly evolving. Therefore, it could be worth reviewing and updating the available safety information on natalizumab.