UPDATE ON NOVEL TREATMENTS IN MS: NATALIZUMAB

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Natalizumab is a humanized monoclonal antibody directed against the α4 subunit of α4β1 and α4β7 integrins, belonging to the new generation of selective adhesion molecule inhibitors. The α4β1 integrin is expressed on the surface of activated T-cells and among these myelin-specific autoaggressive T-cells that are able to penetrate the blood-brain-barrier. When natalizumab binds to the α4 subunit on activated lymphocytes, it prevents α4β1 on the surface of lymphocytes to bind to the vascular cellular adhesion molecule (VCAM-1) on the endothelial cells and thereby inhibits the penetration of these activated T-cells across the blood-brain-barrier into the CNS.

The result of this blockade is a decrease in the number of inflammatory lesions within the brain and spinal cord, clearly expressed as a profound reduction of gadolinium positive lesions on MRI. Natalizumab may also suppress ongoing inflammation in the brain by inhibiting binding of T-cells to osteopontin and fibronectin; although it is uncertain to which degree natalizumab penetrates the blood-brain-barrier.

The effect of natalizumab in MS has been documented in 2 large randomized trials, the AFFIRM and SENTINEL studies. Both studies were placebo-controlled, double blind 2-year trials with a large number of patients.

The AFFIRM study was a randomized, double-blind, placebo controlled, multicenter study comprising 942 patients with relapsing MS. Patients were randomized to treatment with either natalizumab 300 mg or placebo every 4 weeks for 2 years. The primary efficacy outcome was the annual relapse rate in the first treatment year and disease progression after 2 years. The annual relapse rate was reduced by 68% in natalizumab treated patients compared to placebo treated patients, and there was a reduction of 42% in the number of patients with disease progression measured as 1 point or more on the expanded disability status scale (EDSS). The effect on MRI was even more profound. The number of new gadolinium enhancing lesions was decreased by 92% and the number of new lesions on T2-weighted images was reduced by 83%.

In the SENTINEL study patients who on therapy with interferon-beta 1a i.m. had suffered at least one relapse within the last 12 months were randomized to add-on therapy with either natalizumab 300 mg or placebo every 4 weeks for 2 years. Also the SENTINEL study showed a significant reduction in relapse rate and MRI measures of disease activity in the patients with natalizumab as add-on compared to patients with placebo as add-on.

The treatment was well tolerated although a a small number of patients experienced hypersensitivity reactions, of which a few were considered serious anaphylactoid reactions. Approximately 6% of patients developed persistent antibodies that neutralized the therapeutic effect of natalizumab.

Based on the results of the AFFIRM and SENTINEL studies Food and Drug Administration (FDA) approved natalizumab in November 2004. However a few months later 2 cases of progressive multifocal leucoencephalopathy (PML) were described in 2 patients who in the extension of the SENTINEL study were treated with the combination of interferon-beta 1a i.m. and natalizumab. This led to a temporary withdrawal of the drug from the market. After a complete data analysis, and clinical and MRI control of all natalizumab treated patients without finding of additional PML cases, the FDA and EMEA re-approved natalizumab as a second-line treatment in June 2006.

Currently more than 30.000 patients have started treatment with natalizumab and a quantitative risk-benefit analysis of natalizumab concluded that more than a sevenfold increase in the risk of PML was required to decrease the health gain of natalizumab below that of interferon-beta 1a.

However, in July 2008 two new cases of PML in MS patients treated with natalizumab as monotherapy were reported. In both cases PML was diagnosed early in the disease, and both patients survived, one with very few sequelae after PML. Even with the 2 new cases the risk of PML is below the 1:1.000 risk calculated after the 2 initial cases of PML. However, the coming 6-12 months will be decisive for the place of natalizumab in the treatment of MS. At that time we will know if the predicted risk of PML is correct or whether the new 2 cases are only the tip of an iceberg.