

## Adaptive immune responses associated with acute varicella-zoster virus reactivation during treatment with fingolimod

Andrea Harrer, Peter Wipfler, Georg Pilz, Katrin Oppermann, Elisabeth Haschke-Becher, Shahrzad Afazel, Jörg Kraus, Eugen Trinkka and Johann Sellner

Fingolimod, an oral sphingosine 1-phosphate (S1P) receptor modulator, is approved for the treatment of relapsing forms of multiple sclerosis (MS). The interference with S1P signaling leads to retention particularly of chemokine receptor-7 (CCR7) expressing T cells in lymph nodes. The immunological basis of varicella zoster virus (VZV) infections during fingolimod treatment is unclear. Here, we studied the dynamics of systemic and intrathecal immune responses associated with symptomatic VZV reactivation including cessation of fingolimod and initiation of antiviral therapy. Key features in peripheral blood were an about two-fold increase of VZV-specific IgG at diagnosis of VZV reactivation as compared to the previous months, a relative enrichment of effector CD4<sup>+</sup> T cells (36% versus mean 12% in controls), and an accelerated reconstitution of absolute lymphocytes counts including a normalized CD4<sup>+</sup>/CD8<sup>+</sup> ratio and reappearance of CCR7<sup>+</sup> T cells. In cerebrospinal fluid (CSF) the lymphocytic pleocytosis and CD4<sup>+</sup>/CD8<sup>+</sup> ratios at diagnosis of reactivation and after nine days of fingolimod discontinuation remained unchanged. During this time CCR7<sup>+</sup> T cells were not observed in CSF. Further research into fingolimod-associated VZV reactivation and immune reconstitution is mandatory to prevent morbidity and mortality associated with this potentially life-threatening condition.