Lymphocyte subsets show different response patterns to in vivo bound natalizumab--a flow cytometric study on patients with multiple sclerosis.

Abstract:
Natalizumab is an effective monoclonal antibody therapy for the treatment of relapsing-remitting multiple sclerosis (RRMS) and interferes with immune cell migration into the central nervous system by blocking the \( \beta_4 \) subunit of very-late activation antigen-4 (VLA-4). Although well tolerated and very effective, some patients still suffer from relapses in spite of natalizumab therapy or from unwanted side effects like progressive multifocal leukoencephalopathy (PML). In search of a routine-qualified biomarker on the effectiveness of natalizumab therapy we applied flow cytometry and analyzed natalizumab binding to \( \beta_4 \) and \( \beta_4 \) integrin surface levels on T-cells, B-cells, natural killer (NK) cells, and NKT cells from 26 RRMS patients under up to 72 weeks of therapy. Four-weekly infusions of natalizumab resulted in a significant and sustained increase of lymphocyte-bound natalizumab (\( p < 0.001 \)) which was paralleled by a significant decrease in detectability of the \( \beta_4 \) integrin subunit on all lymphocyte subsets (\( p < 0.001 \)). We observed pronounced natalizumab accumulations on T and B cells at single measurements in all patients who reported clinical disease activity (\( n = 4 \)). The natalizumab binding capacity of in vitro saturated lymphocytes collected during therapy was strongly diminished compared to...
treatment-naive cells indicating a therapy-induced reduction of ?(4). Summing up, this pilot study shows that flow cytometry is a useful method to monitor natalizumab binding to lymphocytes from RRMS patients under therapy. Investigating natalizumab binding provides an opportunity to evaluate the molecular level of effectiveness of natalizumab therapy in individual patients. In combination with natalizumab saturation experiments, it possibly even provides a means of studying the feasibility of patient-tailored infusion intervals. A routine-qualified biomarker on the basis of individual natalizumab saturation on lymphocyte subsets might be an effective tool to improve treatment safety.