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Quantification of Arm Exchange in a Therapeutic Antibody: Enabling Improved Dose Monitoring

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Description

The paper "Peptide Mimotope-Enabled Quantification of Natalizumab Arm Exchange during Multiple Sclerosis Treatment" [1] describes the development of an assay that can monitor the concentration of intact natalizumab, a mAb highly effective in treating MS. Natalizumab binds to $\alpha 4\beta 1$ integrin, present on immune cells, and thereby prevents the cells migration from circulation into the central nervous system. Natalizumab is a humanized IgG4 antibody that undergoes arm exchange, where a heavy and associated light chain from one antibody is swapped with that from another, unrelated IgG4 antibody, generating a bispecific antibody that is monovalent for any one epitope [2]. It is hypothesized that the extent of natalizumab arm exchange is dictated by the endogenous IgG4 serum concentration, which has been shown to vary widely between individuals [3]. Importantly, the monovalent bispecific antibody shows a much-reduced affinity for $\alpha 4\beta 1$integrin [4,5]. Thus, individuals taking this therapeutic have, in addition to variations in total natalizumab levels, different proportions of the high potency intact natalizumab and the less potent, arm-exchanged form.

Unfortunately, Progressive Multifocal Leukoencephalopathy (PML) a rare but life-threatening condition, is associated with natalizumab treatment. Although it has been suggested that higher concentrations of natalizumab at nadir increases risk of PML, findings that individuals with low concentrations of natalizumab develop PML indicate that other factors may play a role [6,7]. One hypothesis proposes that increased levels of the more potent intact, non-arm exchanged, natalizumab in patients with relatively low total natalizumab could increase PML risk. The ability of an assay to measure the levels of this more potent form may allow identification of individuals who have increased risk of developing PML. The assay developed leverages a peptide mimotope, discovered by phage display screening that can bind the intact bivalent antibody with similar affinity as that seen for an anti-idiotype antibody [8]. However, although the anti-idiotype antibody can also bind to arm-exchanged monovalent natalizumab (allowing for the measurement of total natalizumab), the mimotope peptide has much lower affinity for arm-exchanged natalizumab and is unable to detect this species. This characteristic enabled the development of two sets of ELISA assays: one of which measures total natalizumab using the anti-idiotype antibody, and one which measures only the intact non-arm exchanged natalizumab using the ELISA assay developed with the mimotope peptide. Thus, it is now possible to retrospectively analyze the serum levels of PML cases associated with low drug levels to determine if increased levels of the more potent intact form of natalizumab was responsible. This unique and straightforward drug monitoring system will provide a more detailed personalized assessment of drug efficacy and risk for those taking natalizumab and aid physicians on important dosing regimen decisions. Therapeutic drug monitoring is an essential yet under-utilized method to create a safe individualized approach for disease management.

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