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Letter to the editor on the paper: "The majority of natalizumab-treated MS patients have high natalizumab concentrations at time of re-dosing"

Erstveröffentlichung in / First published in:

Multiple Sclerosis Journal. 2018, 24(6), S. 820 – 822 *[Zugriff am: 19.08.2019]*. SAGE journals. ISSN 1477-0970.

DOI: https://doi.org/10.1177/1352458517726384

T cells, may be more important in cortical pathology than HLA class II molecules, which present antigens to $CD4^+$ T cells.

We therefore propose to clarify three issues in future studies. First, as Yates et al.[3] did not perform immunostaining of $CD4^+$ T cells, the presence or absence of $CD4^+$ T cells around small cortical veins should be elucidated. Second, the exact location of fibrin(ogen) deposition in the MS cortex remains unclear. It is critical to clarify whether fibrin(ogen) is deposited around small cortical veins. Third, an association of any *HLA class I* gene allele with cortical lesions has never been reported, and therefore, we believe it is worth studying in the future.

In conclusion, our study[2] and Yate's study[3] open a new pathway to study cortical lesion development, highlighting HLA and T cell-mediated mechanisms.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported in part by a Health and Labour Sciences Research Grant on Intractable Diseases (H26-Nanchitou (Nan)-Ippan-043) from the Ministry of Health, Labour and Welfare, Japan, by a Grant-in-Aid for Scientific Research A (MEXT KAKENHI grant no. 16H02657) and C (15K09341), and a Grant-in-Aid for Young Scientists B (17K16125) from the Japan Society for the Promotion of Science, Japan.

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Multiple Sclerosis Journal
2018, Vol. 24(6) 820–822
DOI: 10.1177/1352458517726384

Letter to the editor on the paper: "The majority of natalizumab-treated MS patients have high natalizumab concentrations at time of re-dosing"

Date received: 21 June 2017; revised: 18 July 2017; accepted: 23 July 2017

Van Kempen et al. described high natalizumab concentrations in their natalizumab-treated multiple sclerosis (MS) patients at time of re-dosing.[1] Based on the literature research,[2,3] the authors consider a natalizumab concentration above 2 µg/mL to be sufficient for an adequate alpha-4 integrin receptor saturation of above 70%.

Recently, we have demonstrated similar results using our new cell-based immunoassay to evaluate free natalizumab concentration, cell-bound natalizumab, and alpha-4 integrin receptor saturation as the key pharmacokinetic/pharmacodynamic parameters of natalizumab treatment in different in vivo settings.[4] We investigated the effects of treatment interval extension or treatment cessation.

In line with this study, for all patients treated on the proposed 4-week treatment interval, we could demonstrate natalizumab concentrations above 2 µg/mL (mean, 18.5 µg/mL; standard deviation (*SD*), ±15.3). This was associated with a cell-bound natalizumab relative intensity of 3375 with *SD* of ±1545 by fluorescence-activated

cell sorting (FACS). We could demonstrate that a single natalizumab infusion leads to a 4.7-fold increase in free natalizumab concentration in serum while cell-bound natalizumab increases only 1.4-fold. For patients on longer treatment intervals, we could detect corresponding lower free natalizumab concentrations (5 weeks: 15.84 µg/mL, *SD* ±7.6; 8 weeks: 2.49 µg/mL, *SD* ±0.5). We found that distribution of the free serum antibody in vivo follows comparable rules as of regular immunoglobulin G (IgG) which we could demonstrate by combined cerebrospinal fluid (CSF)/serum analyses. In addition, our analysis could show that free and cell-bound natalizumab were significantly correlated in serum ($r = .49$; $p < .0014$).

Several groups demonstrated an association between body weight and natalizumab binding, although these correlations are only weak.[5,6] Muralidharan et al.[7] found that body weight predicts only a small amount of variability of natalizumab saturation indicating that other yet unknown factors must exist. We have additionally shown that natalizumab has a high binding affinity to alpha-4 integrin and that a significant cell–cell exchange between saturated and unsaturated cells may exist. So, we expect that all cells with available very late antigen-4 (VLA-4) molecules on the surface as potential natalizumab binding sites will impact the amount of free and cell-bound natalizumab. For the peripheral and CSF compartments, we could already demonstrate this link between cell-bound natalizumab and ratio of free natalizumab concentration to cellular concentration.

Different methods to measure natalizumab saturation have been developed.[7,8] We use the ratio of cell-bound natalizumab post-drug to pre-drug infusion. Thereby, we could show statistical significant differences in natalizumab cell-bound levels between different treatment intervals (natalizumab saturation after 4 weeks is 64%, after 5 weeks is 55.2%, and after 8 weeks is 34%), while higher interindividual differences occur with longer treatment intervals. Harrer et al.[9] could demonstrate higher natalizumab saturation levels after a 8-week treatment holiday in 12 patients (CD8 cells, 57%; interquartile range, 26%–64% and CD4 cells, 67%; interquartile range, 38%–69%) with high interindividual variability.

The authors propose a prospective trial investigating longer natalizumab treatment intervals depending on assessment of free natalizumab concentrations. We do not consider the change of infusion interval length as helpful, and we would suggest an individual dose of natalizumab every 4 weeks to keep VLA-4 saturation constant. Further studies may identify optimal VLA-4 saturation levels that lead to effective MS treatment without increasing risk of progressive multifocal leukoencephalopathy (PML). Until that, we should monitor VLA-4 saturation to not over treat MS patients and keep PML risk low.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Multiple Sclerosis Journal
2018, Vol. 24(6) 822–823
DOI: 10.1177/1352458517734073

Response to "Letter to the editor on the paper: The majority of natalizumab-treated MS patients have high natalizumab concentrations at time of re-dosing"

Date received: 29 August 2017; accepted: 3 September 2017

With great interest we have read the comment of Sehr et al.[1] on our study: The majority of natalizumab-treated MS patients have high natalizumab concentrations at time of re-dosing.[2]

In our research, we find similar results as earlier presented by Sehr et al.,[3] a mean natalizumab trough concentration in a 4-week infusion interval above 15 µg/mL and a large variation inter-individually but stable concentrations intra-individually.[2] The study of Sehr et al.[3] complements our results with cell-bound natalizumab and alpha-4 integrin receptor saturation data.

As inter-individual free natalizumab concentrations can widely differ between patients, we fully agree with Sehr et al. that personalized-based natalizumab treatments should be explored in clinical trials. When considering personalizing natalizumab treatment, there are two relevant options: to alter the dose to the individual patient or to alter the infusion interval. Although both options should be explored, we would like to underline the patients' interest; a personalized infusion interval will decrease the frequent hospital visits and therefore may likely increase the patients' quality of life. Also, fewer hospital visits will decrease hospital costs.

Natalizumab blocks alpha-4 integrin, and the concentration of natalizumab just before the next infusion will be most critical with respect to blocking capacity. Both interval prolongation and dose reduction will result in reduced trough levels, and one option is not a priori preferred over the other with respect to saturation of alpha-4 integrin.

If the natalizumab concentration is an important factor in relation to receptor blocking, there is room for individualized dosing regimens, given that standard dosing results in substantial variation in natalizumab trough levels. It is this variation that could be explored in order to arrive at dosing schemes tailored to the individual patient. We expect receptor saturation an important parameter in this respect, which we anticipate to be correlated with concentrations of serum natalizumab.

Sehr et al. opt for a personal dose–dependent treatment and address an important point that alpha-4 integrin receptor saturation should be constant and not drop with longer infusion intervals. Muralidharan et al.[4] showed in extensive data on natalizumab pharmacokinetics and pharmacodynamics that alpha-4 integrin saturation overall stayed above 80% if free natalizumab concentration was above 10 µg/mL. When the infusion interval is concentration-guided and trough concentration is kept above 10 µg/mL, the saturation is expected to remain stable (above 80%). The extent to which a receptor saturation of >70%–80% is required for optimal drug efficacy remains poorly investigated; the patients described by Sehr et al. receiving a 5-week infusion interval ($N=18$) and a 8-week infusion interval ($N=18$) were clinically stable with a mean trough receptor saturation of 55.2% and 34%, respectively.

In conclusion, we would like to thank Sehr et al. for their interesting comment. We agree that personalized natalizumab treatment should be explored in clinical trials, either by a personalized dose or altered infusion interval, given that free natalizumab concentration remains above a certain threshold to maintain stable alpha-4 integrin receptor saturation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Z.L.E.v.K. has no conflicts of interest. T.R. has received speaking fees from Pfizer and AbbVie. J.K. has received speaker and consulting fees from Merck-Serono, Biogen Idec, TEVA, Genzyme, Roche and Novartis.