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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"

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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

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