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*Letter to Editor*

# Comparison of nadir serum concentrations in the extended dosing therapy of natalizumab between American and Japanese multiple sclerosis patients

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Natalizumab, a humanized monoclonal antibody against very late antigen-4 (VLA-4), inhibits the transmigration of immune cells across the blood-brain barrier into the central nervous system (CNS).[1] However, progressive multifocal leukoencephalopathy (PML) is caused following natalizumab treatment in patients with relapsing–remitting multiple sclerosis (RRMS). The reason for higher PML prevalence in patients treated with natalizumab in Europe than those in the USA patients may not be the more frequent use of cytotoxic medications in Europe, but may be the lower body weight (BW) of European patients and higher nadir serum concentrations of natalizumab.[2] We recommended BW-based natalizumab therapy in RRMS patients because a linear relation exists between serum concentrations and BW (50–110 kg) ($y = -0.5363x + 75.71$, $R^2 = 0.846$).[2] Recently, extended interval dosing of natalizumab therapy has been shown.[3]

We calculated mean nadir serum concentrations in American (mean BW: 72 kg) and Japanese (57.6 kg) patients with RRMS treated with extended interval dosing of natalizumab (8–16 week intervals). We used formulas of pharmacology to calculate the maximum serum concentration ($C_{max}$) after steady state using accumulation factor.[4] The $C_{max}$ (mean ± standard deviation: 84.8 ± 22.3 μg/ml and 121.4 ± 22.3 μg/ml, respectively) and elimination half-time ($t_{1/2}$) (249 ± 105 h and 365 ± 132 h, respectively) after single administration of natalizumab were obtained from each clinical trial (C-1801 and phase IIa study, respectively).

$C_{max}$ is higher and $t_{1/2}$ is longer in Japanese patients ($n = 12$) than in American patients ($n = 20$), causing higher nadir serum concentrations during steady state in Japanese patients (mean: 47.0 μg/ml) than in American patients (15.3 μg/ml) treated with monthly administrations of natalizumab. Mean nadir serum concentrations during extended interval dosing of natalizumab in American and Japanese patients were 2.01 and 11.0 μg/ml with an 8-week, 0.78 and 5.19 μg/ml with a 10-week, 0.30 and 2.69 μg/ml with a 12-week, and 0.05 and 0.74 μg/ml with a 16-week interval, respectively. Our results were obtained using mean values, and patients with higher BW may show lower concentrations and may have more risks of relapses than those with lower BW with extended interval dosing therapy.

Although serum concentrations of more than 5.0 μg/ml lead to a plateau value of VLA-4 saturation[5] and we do not have direct evidence that higher $C_{max}$ or longer $t_{1/2}$ is related to the risks of PML, we have concerns that excess concentrations of natalizumab may affect immune surveillance in the CNS and increase the risk of PML. We also think American patients treated with more than an 8-week interval of natalizumab have a risk of relapse because at least 3 μg/ml is needed to keep VLA-4 saturation levels at more than 70%, which has been shown to be associated with continued therapeutic efficacy (Biogen Idec, data on file).[5]

We do not exclude the possibility of factors related to the metabolism of natalizumab other than BW, but we believe that the same protocol of natalizumab administration for all patients may be insufficient and that adequate dosing such as BW-based dosing may be needed.

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## Conflict of interest

Dr Tanaka received speaker honoraria from Biogen Idec Japan and Tanabe Mitsubishi. Kaho Yokoyama has nothing to declare.

## References

1. Schwab N, Schneider-Hohendorf T and Wiendl H. Therapeutic uses of anti-α4-integrin (anti-VLA-4) antibodies in multiple sclerosis. *Int Immunol* 2015; 27: 47–53.
2. Tanaka M, Kinoshita M, Foley JF, et al. Body weight-based natalizumab treatment in adult patients with multiple sclerosis. *J Neurol* 2015; 262: 781–782.
3. Bomprezzi R and Pawate S. Extended interval dosing of natalizumab: A two-center, 7-year experience. *Ther Adv Neurol Disord* 2014; 7: 227–231.
4. Winter ME. *Basic clinical pharmacokinetics*, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2010.
5. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology* 2009; 72: 402–409.