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LETTER TO THE EDITORS

Anti-natalizumab antibodies during 8 years of natalizumab treatment: effect on natalizumab concentration and α4-integrin receptor saturation

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Dear Sirs,

Natalizumab targets the α4-integrin receptor on lymphocytes and effectively decreases inflammation in relapsing remitting multiple sclerosis (RRMS) [1]. Comparable to many protein therapeutic agents, natalizumab can induce antibodies [2–5].

Here, we present a case of high-titer antibodies during 8 years of natalizumab treatment and the possible ongoing therapeutic effect despite rapid decline of natalizumab concentration and receptor saturation after natalizumab infusion.

A 39-year-old woman was diagnosed with RRMS in 2007. She had active disease under treatment with interferon beta-1a after which she started natalizumab treatment in September 2009. During the initiation and continuation of natalizumab, she did not experience infusion-related reactions. The patient was relapse free during natalizumab treatment; however, she did experience occasional fluctuations of previous symptoms. There were no new/enlarging T2 lesions on the annual brain MRI (2009–2017) or the MRI of the spinal cord (2009 and 2016). At natalizumab initiation, the EDSS score was 4.0 which improved to 3.0 at year 2 after which the EDSS remained stable (tested in years 2, 3, 4 and 8).

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In 2017, natalizumab trough concentration was measured [6], which was 0.1 µg/ml (very low). The patient tested positive for anti-natalizumab antibodies with a high titer (> 9500 AU/ml). Natalizumab concentration and CD8 α4-integrin receptor saturation were measured over a 4-week cycle after natalizumab infusion in comparison to a matched control (Fig. 1). Retrospectively, we tested natalizumab concentration and antibodies in stored serum 3 and 12 months after starting natalizumab. At both time points, trough concentrations were very low and antibodies were high (> 1700 AU/ml).

After discovering the high-titer anti-natalizumab antibodies, natalizumab was discontinued in July 2017. After 9 months, the patient experienced pain behind the left eye accompanied by blurry vision. Neurological examination showed a left relative afferent pupil defect. The patient had never experienced an optic neuritis before and a visual evoked potential showed significant prolongation of p100 latency of the optic nerve tract on the left. The patient was treated with a 3 day course of methylprednisolone after which there was a gradual recovery. On follow-up of brain MRI after 3, 6 and 10 months of treatment discontinuation, no active T2 lesions or gadolinium-enhancing lesions were seen (the last scan included the spinal cord). Due to the optic neuritis after discontinuation of natalizumab, the patient started fingolimod treatment in September 2018. The EDSS score remained stable (3.0).

Anti-natalizumab antibodies are associated with recurrence or persistence of disease activity and with infusion-related reactions [2, 5, 7]. These antibodies are often transient [5], with 3.5–9.4% of patients having persistent antibodies [2–5]. A high antibody titer at start of natalizumab therapy predicts the persistence of anti-natalizumab antibodies [8], which is in agreement with our patient who retrospectively had high titers of anti-natalizumab antibodies 3 months after treatment initiation. Anti-natalizumab

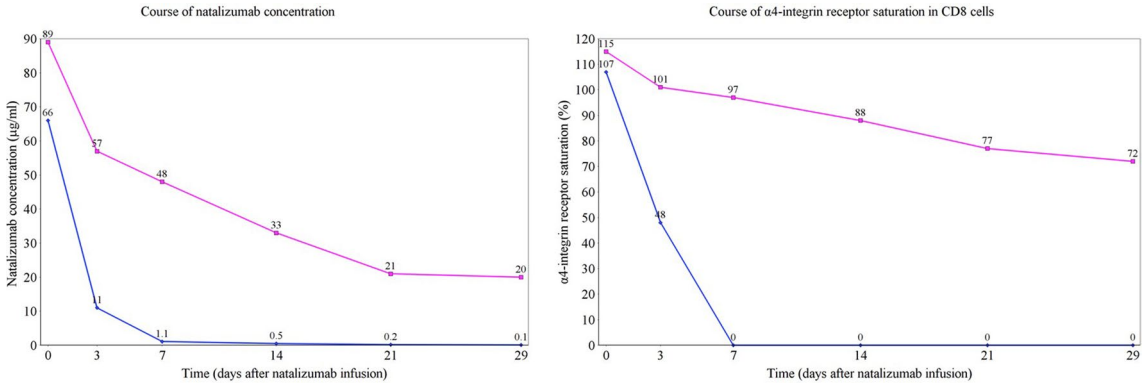

Fig. 1 Longitudinal results of natalizumab concentration and α4-integrin receptor saturation on CD8 cells. 4-week cycle of natalizumab concentration after infusion. Blue line (triangles) represents the patient with anti-natalizumab antibodies and the red line (squares) represents the matched control (matched for gender, age and treatment duration). The first concentration/α4-integrin saturation is measured 1 h after natalizumab infusion. Natalizumab concentration was tested using a cross-linking assay using polyclonal rabbit anti-natalizumab F(ab)2 fragments for capture and a mouse anti-IgG4 monoclonal antibody for detection [6]. For testing α4-integrin saturation, peripheral blood mononuclear cells (PBMCs) were isolated from citrated blood samples and natalizumab binding to α4-integrin on CD8 effector and effector memory cells was analyzed by flow cytometry. To obtain a completely saturated reference sample, PBMCs were post-saturated with saturating concentrations natalizumab for 15 min at room temperature, followed by extensive washing with PBS to remove natalizumab excess, after which they were analyzed by flow cytometry for maximum natalizumab binding by anti-human IgG4. Natalizumab binding was expressed as percentage relative to saturated condition for each sample. CD4 and CD8 cells were both assessed with comparable results. Both measurements (concentration and saturation) were performed at Sanquin Laboratory, Amsterdam, the Netherlands

antibodies titers are inversely correlated with serum natalizumab concentrations [2, 5], as our case illustrates. Usually, natalizumab receptor desaturation (< 50%) occurs after approximately 8 weeks after the last infusion [9], which is in strong contrast to our patient, in whom receptor desaturation took place within 3 days. After receiving these results, we assumed the absence of disease activity was due to the natural course of the disease in our patient. However, the relapse after discontinuation suggests that despite rapid reversal of pharmacokinetic and pharmacodynamic measures after infusion, there might still be a remaining therapeutic effect of natalizumab, although especially in an unpredictable disease like MS, with this one case no causality can be proven.

To our knowledge, we are the first to describe pharmacodynamics and pharmacokinetic results during a 4-week natalizumab cycle in an antibody-positive patient which show the rapid decline of natalizumab concentration and α4-integrin receptor saturation. Our report suggests that despite the presence of high-titer anti-natalizumab antibodies, natalizumab might still have a therapeutic effect.

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Compliance with ethical standards

Conflicts of interest Z. van Kempen, J. van Rossum, D. Doesburg, A. de Vries, I. Claessen, A. de Vries and B. van Oosten: nothing to report. T. Rispens: has received speaking fees from Pfizer and AbbVie. J. Killestein: has received speaker and consulting fees from Merck-Serono, Biogen Idec, TEVA, Genzyme, Roche and Novartis.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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