


## Time to talk about timing – when to start, stop and change anti-migratory drugs in MS

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Multiple sclerosis (MS) is an inflammatory disease, and the relapsing–remitting form of MS (RRMS) is widely considered to be the most inflammatory phenotype of MS. There are currently eight approved therapies for patients with RRMS. Not surprisingly, all of these medications are anti-inflammatory. The mechanisms of action of agents that were approved in the 1990s are not completely understood. Newer drugs, including fingolimod and natalizumab, are the result of rational drug design that targets specific molecules. Fingolimod is a structural analog and a functional antagonist of sphingosine-1-phosphate (S1P), which mediates the egress of lymphocytes from the lymph nodes.<sup>1</sup> Natalizumab is a recombinant humanized monoclonal antibody that targets  $\alpha 4$ -integrin, which is part of several heterodimeric adhesion molecules that promote leukocyte adhesion to blood vessels and extracellular matrix molecules.<sup>2</sup> Both agents are very effective in decreasing the number of MS relapses and in diminishing the number and volume of new disease lesions on magnetic resonance imaging (MRI).<sup>3–6</sup> There is no evidence that either agent alters the etiological factors that cause MS disease activity. Instead, both agents appear to sequester some of the autoreactive lymphocytes out of the brain and spinal cord.

One question of great clinical relevance is whether sequential therapy of natalizumab and fingolimod results in stable disease activity and clinical improvement, or whether there is worsening of MS signs and symptoms. In the current issue of this journal, several investigators address this issue and present data from case reports and small case series.

Hakiki and colleagues<sup>7</sup> describe six patients with MS who had previously been treated with fingolimod, and who experience disease reactivation on cessation of therapy. One patient described by Hakiki et al.<sup>7</sup> appeared to have developed disease rebound after fingolimod had been discontinued for three months. Thus, it has to be assumed that fingolimod was completely washed out at that point.

Results from a case series by Rinaldi et al.<sup>8</sup> published in this issue support the observations by Hakiki and colleagues. Here, 22 JC virus (JCV)-positive natalizumab-treated RRMS patients who were shifted to fingolimod after a three-month washout were assessed. In the nine-month-follow up period, MS reactivation was observed in 11/22 patients, and a possible disease rebound was observed in three patients.

As the natalizumab experience has taught us, disease rebound is very difficult to verify. In a clinical setting the documentation of disease activity prior to the initiation of a new pharmacotherapy is incomplete. Patients are not always seen by a neurologist when they experience a neurological problem, and MR images of the brain are not obtained. Consequently, re-occurring clinical or paraclinical disease activity after discontinuation or switch of a therapy may lead to an over-estimation of relapses and new MRI lesions. Some investigators have reported rebound of disease activity after cessation of natalizumab therapy.<sup>9–12</sup> However, the occurrence of a true disease rebound after natalizumab as a frequent phenomenon has since been called into question. O'Connor and colleagues analyzed clinical relapses in 1866 patients and gadolinium-enhancing MRI lesions in 341 MS patients who had discontinued natalizumab.<sup>13</sup> While there was an increase in the annualized relapse rates and in the number of gadolinium-enhancing lesions after cessation of natalizumab that peaked between four and seven months, a rebound of relapse or MRI lesion activity was not observed in any of the analyses conducted.<sup>13</sup> Similar data do not exist for fingolimod. However, the work by O'Connor et al. should caution us not to over-interpret re-emerging disease activity after fingolimod discontinuation as disease rebound. In addition, the work by O'Connor et al. also shows that MS disease activity prior to initiation of natalizumab therapy may be a strong predictor of disease activity following cessation of treatment: Patients with a high relapse rate before initiation of natalizumab therapy appear to have the highest risk of disease re-activation, whereas patients with a low relapse rate have a low risk.<sup>13</sup> We speculate that the same is true in patients who are being treated with fingolimod. We would not be surprised if the MS patient described by Hakiki et al. and Rinaldi et al. who experienced reactivation of the disease three months after termination of fingolimod had had more disease activity than the five patients prior to starting this agent.

Jander and colleagues<sup>14</sup> describe an MS patient who developed a clinical attack that had MRI characteristics consistent with tumefactive demyelination after switching therapy from natalizumab to fingolimod. This is interesting, as tumefactive demyelination typically occurs at disease onset, and only very rarely in established disease. Interestingly, another case of tumefactive MS in a

patient on fingolimod was recently reported by Visser et al.<sup>20</sup>

Another case report in this issue by Daelman et al.<sup>15</sup> describes a woman with MS who developed new neurological signs and symptoms during a three-month treatment hiatus between the cessation of natalizumab and the initiation of fingolimod. This is also an important observation.

Recent analyses suggest that MS subpopulations can be stratified into patients with lesser or greater progressive multifocal leukoencephalopathy (PML) risk based on the presence of three risk factors: (1) natalizumab treatment duration, (2) prior immunosuppressant use and (3) anti-JCV antibody status.<sup>16</sup> Therefore, exit strategies are needed for MS patients on natalizumab at high risk for developing PML. The ideal exit strategy from natalizumab would prevent disease reactivation after its discontinuation, yet substantially lower the risk of developing PML. These two goals are not easily accomplished, as the efficacy of natalizumab and other MS therapies, including fingolimod, may very well be associated with their capability of decreasing immunosurveillance of the central nervous system (CNS). A reduction of CNS immunosurveillance may also increase the susceptibility to PML.

To maneuver this therapeutic dilemma of safety and efficacy, clinical neurologists currently have no strong clinical evidence or biomarkers. Daelman et al.<sup>15</sup> appear to have favored patient safety over potential drug efficacy when they decided to not treat their patient for several months. It is possible that this delay may very well have resulted in the clinical exacerbation that is described. Again, based on the data by O'Connor et al.,<sup>13</sup> a clinical rebound after discontinuation of natalizumab has to be considered an extremely rare event, one that likely requires redistribution of pro-inflammatory leukocytes into the CNS. Natalizumab therapy may lead to sequestration of pro-inflammatory cells into the peripheral blood. Krumbholz et al.<sup>17</sup> demonstrated that natalizumab therapy increased immature and mature CD19<sup>+</sup> B cells in peripheral blood. Kivisakk et al.<sup>18</sup> showed that the frequency of peripheral blood CD4<sup>+</sup> T cells producing interferon gamma (IFN $\gamma$ ), tumor necrosis factor and interleukin (IL)-17 upon anti-CD3 stimulation increased six months after initiation of natalizumab treatment and remained elevated throughout the follow-up. The frequency of CD4<sup>+</sup> T cells expressing CD25, human leukocyte antigen (HLA)-DR and CCR6 ex vivo was increased at one or more time points during treatment. As a consequence, it has to be assumed that some of these cells may be encephalitogenic and may gain access to the CNS in some patients in whom natalizumab is discontinued. While fingolimod affects the mobilization of T cells from the lymph nodes, it has no known effects on T cells already in the peripheral circulation, and it has only minimal effects on B cells in the CSF. For neither agent is it known what effect sequential combination therapy has on regulatory lymphocytes or cytokine networks.

There may be an alternative explanation for disease rebound described by Daelman et al.<sup>15</sup> The reported patient was switched from natalizumab to fingolimod. After not being treated with any agent for 2.5 months, she developed a clinical relapse. After 3.5 and 4.5 months of discontinuing natalizumab, fingolimod treatment was initiated and discontinued. Just a few days later, a relapse occurred. The enhanced disease activity following fingolimod discontinuation compared to the period before fingolimod initiation raises the question whether fingolimod exerts a pro-inflammatory activity on the immune system that occurs only (1) when the drug is discontinued, or (2) in the early treatment phase, during which the anti-migratory activity of the drug is not fully achieved. The occurrence of severe relapses after initiation of fingolimod has been observed in a few cases. Castrop and colleagues<sup>19</sup> reported a severe relapse in an MS patient who was switched from interferon beta to fingolimod. The patient developed the relapse with multiple gadolinium-enhancing lesions within six weeks on fingolimod therapy despite a substantial reduction in the number of peripheral CD4<sup>+</sup> T cells and B cells.

To summarize the observations by Hakiki,<sup>7</sup> Rinaldi,<sup>8</sup> Jander,<sup>14</sup> Daelman<sup>15</sup> and their colleagues: It is very likely that neither fingolimod nor natalizumab alter the autoimmune response underlying MS, but sequester it out of the CNS. Therefore it does not seem reasonable to stop either or both drugs without offering alternative therapies. The timing of sequential pharmacotherapies that involve fingolimod and natalizumab becomes an increasingly important issue with the wider use of these agents. Clinical trials are warranted to test different treatment paradigms, including no natalizumab wash-out, or even an intermittent overlap of both agents. Leaving patients untreated does not seem to be a reasonable strategy.

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