

Review on PML Risk Stratification in Natalizumab-Treated Multiple Sclerosis Patients

Natalizumab ile Tedavi Edilen Multipl Skleroz Hastalarında PML Risk Değerlendirmesi

Nikolaos C. GRIGORIADIS

Laboratory of Experimental Neurology and Neuroimmunology, 2nd Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Macedonia, Greece

ABSTRACT

Natalizumab (NAB) is the first approved among the monoclonal antibodies tested for the treatment of relapsing forms of multiple sclerosis (MS). However, despite the high effectiveness of this drug in MS, the risk of JCV infection within the central nervous system (CNS) leading to progressive multifocal leukoencephalopathy (PML), a potentially lethal condition, is of high concern. Consequently, attempts to stratify patients treated with NAB into those of higher or lower risk for developing PML are urgent. For the time being, three key factors seem to determine the risk of PML: treatment duration beyond 24 months, prior immunosuppressive therapy and the serum anti-JCV antibody detection. Clearly, serum JCV antibody detection represents a tool for PML risk stratification in MS patients treated with NAB. The large variety of methods published so far has resulted in controversies with regard to JCV seroprevalence. However, a standardized assay is now available. (*Archives of Neuropsychiatry 2011; 48 Supplement 2: 61-3*)

Key words: Multiple sclerosis, natalizumab, PML, risk stratification

ÖZET

Natalizumab (NAB) yineleyici multipl skleroz (MS) formları için denenen monoklonal antikorlar arasında ilk onay alandır. Ancak, bu ilacın MS'deki yüksek etkinliğine rağmen merkezi sinir sisteminde (MSS) JCV enfeksiyonu sonucu ölümcül olabilen progresif multifokal lökoensefalopati (PML) ortaya çıkma riski ciddi kaygı yaratmaktadır. Bunun sonucunda NAB tedavisi alan hastaların PML gelişimi açısından yüksek riskli veya düşük riskli olarak belirlenmesi acil önem taşımaktadır. Bugünkü bilgilerle üç ana faktörün PML riski açısından belirleyici olduğu düşünülmektedir: tedavi süresinin 24 ayı aşması, daha önceden immunsupresif tedavi kullanılması ve serumda anti-JCV antikorlarının saptanması. Aşıkardır ki, serum JCV antikorlarının saptanması NAB alan hastalarda PML risk katmanlanması için önemli bir gereçtir. Bugüne dek yayınlanmış olan çok çeşitli yöntemler JCV seropozitivitesi açısından çelişkili sonuçlar yaratmıştır. Ancak artık standardize edilmiş bir test mevcuttur. (*Nöropsikiyatri Arşivi Özel Sayı 2: 61-3*)

Anahtar kelimeler: Multipl skleroz, natalizumab, JCV, PML, risk katmanlanması

Introduction

Natalizumab (NAB) is a recombinant humanized monoclonal anti- α 4-integrin antibody (1,2). It works by interfering with the migration of inflammatory cells into the central nervous system (CNS) through the blood-brain barrier. It has been approved as a treatment of relapsing-remitting MS (RRMS) patients who either fail therapy with interferons or exhibit highly active relapsing-remitting disease. Consequently, NAB is considered as either a second- or first-line treatment for relapsing MS cases, respectively. There is clear evidence from placebo-controlled phase III clinical studies that monthly infusion of NAB resulted in reduced relapse rate, MRI-cerebral lesion load, gadolinium-enhancing lesions, and disability progression (3,4). Interestingly enough, post-hoc analysis of data from the AFFIRM study

indicated that NAB treatment resulted in a significant proportion of patients exhibiting absence of disease activity as defined by clinical or radiological criteria or a composite of the two (5).

The overall incidence of serious adverse events associated with NAB treatment seems to be low. However, an increased concern on the safety of the treatment with NAB was noticed due to adverse events with particular notice to the occurrence of progressive multifocal leukoencephalopathy (PML), which was fatal in some cases. PML usually occurs following active replication of the human polyoma JCV in glial cells of the brain when an immune system becomes compromised, resulting in lytic death of oligodendrocytes and subsequent demyelination (6,7). Noteworthy, as of June 1, 2011, 24 of 133 (18%) NAB-treated patients with PML had died. The 109 surviving individuals have varying levels of disability, ranging from mild to severe (8).

Address for Correspondence/Yazışma Adresi: Dr. Nikolaos C. Grigoriadis, Laboratory of Experimental Neurology and Neuroimmunology, 2nd Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Macedonia, Greece

E-posta: grigoria@med.auth.gr

However, it is noteworthy that NAB-associated PML has improved survival compared with PML in other populations (9).

It is now pretty clear that early identification of PML signs and symptoms is crucial for the as best as possible outcome for patients affected by this disorder. Although beyond the aim of the present review, some key points with regard to the diagnosis, management and consequences for the patient thereafter are essential. Intensive monitoring of patients undergoing NAB treatment increases the possibility that JCV infection would be identified at its initial stages. Indeed, early diagnosis through enhanced clinical vigilance and optimal management of PML may improve outcomes, according to data presented at theECTRIMS/ACTRIMS 5th Joint Triennial Congress.

NAB-associated PML had better survival compared with PML in other populations. Improved survival was associated with younger age at diagnosis, less disability (lower EDSS scores) prior to PML, more localized disease on brain MRI, shorter time from symptom onset to PML diagnosis. Disability in survivors ranged from mild to severe. In survivors with > 6 months follow-up, 33% had mild, 33% had moderate and 33% had severe disability. These data suggest that earlier diagnosis through enhanced clinical vigilance and aggressive management of PML may improve outcomes. Of 159 PML cases identified in the post-marketing setting, 130 patients were still alive as of September 1, 2011 (82% survival rate). In survivors with more than six months of follow-up, 13% had mild disability, 47% had moderate disability, and 40% had severe disability (10).

In addition, routine MRI monitoring is vital to discriminate PML from MS. Moreover, cerebrospinal fluid (CSF) PCR analysis for JCV is important to diagnose PML. However, sensitive assays are needed on the basis that the number of NAB-associated PML cases is low, and therefore false-negative results can occur. In cases where CSF analysis with PCR is not diagnostic, a brain biopsy procedure might be needed whenever JCV infection cannot be ruled out (11).

Individuals with NAB-associated PML should be treated with plasma exchange to remove the drug and reconstitute their immune system (12). However, there is an increased risk for patients to develop immune reconstitution inflammatory syndrome (IRIS) (13). The underlying mechanism in IRIS is considered a T-cell-mediated process and therefore, high-dose corticosteroid administration seems beneficial.

Evidently, considering the rather complicated cascade of events following the occurrence of JCV infection, the need for safe management of PML cases among NAB-treated MS patients is crucial in order to minimize the potentially lethal consequences. Most importantly, on the basis of Hippocrates' quote "to do good or to do no harm", PML risk stratification is urgent, since disease prevention and risk reduction are critical due to the absence of any effective antiviral therapy for PML.

Currently, three factors are considered to play a role in the risk of PML occurrence: duration of NAB dosing, previous treatment with immunosuppressant agents before receiving NAB, and serum anti-JCV antibody status (8).

NAB Treatment Duration

Following the restricted approval of the drug in 2006 and the risk minimization plans that followed, such as the Tysabri Outreach Unified Commitment to Health (TOUCH), the Tysabri Global Observation Program Safety (TYGRIS), etc., the first systematic review of all patients included in those studies estimated the risk of PML to be 1:1000 after an average treatment time of about 18 months (14). A more recent systematic analysis of risk based on the first 28 reported PML cases since the remarketing of NAB in June 2006 indicated that the incidence of PML increased with duration of therapy from approximately 0.11/1,000 (95% CI, 0.023-0.285, in patients with less than 12 infusions to 0.53/ 1,000 (95% CI, 0.30-0.75) in patients with 13-24 infusions, and even to 0.99/1,000 (95% CI, 0.73-1.00) after 25-36 infusions (15).

In an attempt to identify the exact time when PML is more likely to occur, then one may safely speculate that the first year of treatment may not be the case, since if the opposite might be valid, then the number of potential PML cases among the patients treated with NAB for 12 months or more might nowadays be more than 55000. However, there is current evidence that the risk of PML rose in individuals with more than 24 infusions of NAB, including those receiving the drug in clinical trials (post reintroduction) and combined worldwide post-marketing exposure up to May 31, 2011. In the most recently updated review (8), it is reported that among NAB-treated MS patients, PML risk might plateau (or even reduced?) with longer than 2 years treatment. However, such an interpretation may not be absolutely evidence-based since available data for this time are small. Overall, the duration of NAB dosing before PML diagnosis ranged from about 1 year to more than 3-5 years (mean 2 years) (8).

Previous Exposure to Immunosuppressants

After the initial NAB approval, three patients undergoing NAB therapy in combination with other immunoregulatory and immunosuppressive agents were the first to be diagnosed with PML (16,17,18). The agent was later indicated as monotherapy in patients with relapsing forms of MS. Since then, additional cases of PML were reported in patients with MS receiving NAB as monotherapy (15,19,20,21), thereby, indicating that the concomitant administration of NAB and immunomodulators or immunosuppressants is not the prerequisite of PML development. However, it has gradually been identified that NAB-treated patients previously exposed to immunosuppressants are at 3-4 times higher risk of developing PML than those who have never been before under immunosuppression (4).

Moreover, when the both factors, i.e., NAB-treatment duration and previous exposure to immunosuppressants, are considered, the risk ranges from 0.66/1000 patients, if 24 or fewer monthly infusions are administered, up to 4.30/1000 patients, in those treated for 25-48 months (8).

Anti-JCV Antibody Status

The necessity to further investigate the mechanisms that predispose certain patients to an increased risk of developing PML while receiving NAB therapy was evident particularly when the first 31 confirmed PML cases were recorded.

Potential biological markers aiming at the early identification of patients at lower or higher risk for developing PML were evidently important to allow more appropriate use of NAB. In line with this, detection of serum anti-JCV antibodies are expected to be a sensitive marker since infection by JCV is a prerequisite for PML development. Moreover, anti-JCV antibodies may also distinguish current or past infection with JCV. Indeed, a recently published study has suggested that presence of JCV DNA in peripheral body fluids may be useful for stratification of PML risk (22).

The recently established anti-JCV antibody 2-step ELISA assay is now considered as a potential tool for stratifying MS patients for risk of developing PML (8). The utility of this assay is also supported by the low (2.5%) false-negative rate (23). It has also been reported that anti-JCV antibody status seems to be stable over time, with a less than 2-3% annual seroconversion rate (24).

In a more recent paper, additional biological markers in risk stratification under monoclonal antibody immunotherapy of autoimmune disorders are suggested (25). The authors reported that strongly reduced iATP is a bioenergetic parameter of CD4+ T-cell function in monoclonal antibody-associated PML-patients and patients with opportunistic CNS infections. In particular, a decrease of iATP in MS patients treated with NAB for more than 24 months has also been reported. The assessment of anti-JCV antibodies together with the longitudinal determination of iATP levels has been suggested to constitute a clinically useful strategy (26). However, whether this assay may be a valuable tool for PML stratification in NAB-treated MS patients needs further investigation.

Estimation of PML Risk

In a recent review based on meetings between several independent committees, (8) estimation of PML risk and relevant algorithm on the basis of all three factors, i.e. the duration of NAB dosing, previous treatment with immunosuppressant agents before receiving NAB and the serum anti-JCV antibody status, has been reported.

In particular, patients who tested negative for anti-JCV antibodies represent the lowest risk group (≤ 0.11 per 1000; 95% CI 0.00-0.59) in the PML risk-stratification algorithm. However,

patients treated with NAB for 25-48 months, who received immunosuppressant drugs before initiation of NAB, and tested positive for anti-JCV antibodies are at greatest risk (7.80 per 1000; 95% CI 5.20-11.30) of developing PML. Patients who were positive for anti-JCV antibodies and had not used immunosuppressants before, irrespective of treatment duration, may exhibit a PML risk consistent with that in the overall NAB-treated patients (0.35 per 1000; 95% CI 0.19-0.60 for a treatment period of 1-24 months and 2.50 per 1000; 95% CI 1.80-3.40 for a treatment period of 25-48 months). PML incidence in patients positive for anti-JCV antibodies was calculated on the basis of the assumptions that 55% of NAB-treated MS patients are positive for anti-JCV antibodies, the proportion of NAB-treated patients with previous immunosuppressant use was 20% (TYGRIS), and 100% of confirmed cases of PML were positive for anti-JCV antibodies before onset and diagnosis of PML.

Future large-scale studies will validate the proposed PML risk stratification among NAB-treated MS patients and will thus contribute to a higher safety profile of an otherwise highly effective disease-modifying drug.

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