Journal of Neuroimmunology 277 (2014) 6–12

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Immunological biomarkers identifying natalizumab-treated multiple sclerosis patients at risk of progressive multifocal leukoencephalopathy

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ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form 27 October 2014
Accepted 29 October 2014

Keywords:
Multiple sclerosis
Natalizumab
Progressive multifocal leukoencephalopathy
T-cell receptor excision circles
K-deleting recombination excision circles
T-cell receptor repertoire

ABSTRACT

Natalizumab-induced progressive multifocal leukoencephalopathy appears to be unleashed by complex interactions between viral and immunological host factors leading the latent form of JC virus to become pathogenic. Positive anti-JC virus antibody status, prior use of immunosuppressants, and increasing duration of natalizumab treatment have been proposed as risk factors for progressive multifocal leukoencephalopathy in multiple sclerosis patients, but while they may help to identify the most appropriate patients for natalizumab, their use have some limitations. Therefore, a large body of studies is ongoing to identify alternative, reliable immunological markers capable to improve the safety and efficacy of therapy, and to guide tailored clinical decisions.

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1. Introduction

Several disease-modifying therapies that appear to be more efficacious than interferon beta 1b, which was the first drug proven to be effective in altering the natural history of the disease (The IFNB Multiple Sclerosis Study Group, 1993; Karussis, 2013), have been recently proposed for the treatment of relapsing–remitting multiple sclerosis (MS). The so far approved disease-modifying drugs, although showing variable efficacy in reducing relapse risk and preserving neurological

Abbreviations: CDR3, complementarity-determining region-3; CNS, central nervous system; CSF, cerebrospinal fluid; iATP, intracellular ATP concentration; JCV, JC virus; KRECs, K-deleting recombination excision circles; miRNA, microRNA; MRI, magnetic resonance imaging; MS, multiple sclerosis; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; TCRBV, T-cell receptor V beta family; TRECs, T-cell receptor excision circles.

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http://dx.doi.org/10.1016/j.jneuroim.2014.10.011
0165-5728/

functions, differ in tolerability, likelihood of treatment adherence, risk of major toxicity, and are associated to adverse effects of variable severity (Wingerchuk and Carter, 2014).

Thus, the benefit-to-risk ratio for each alternative treatment must be carefully evaluated at multiple levels when a therapeutic strategy has to be chosen. Several factors should be taken into account for the prescription of immunoactive drugs, such as severity and worsening of the disease, patient's concern about present or future symptoms and disability, patient's tolerance to side effects, availability of other therapeutic options, and existence of biomarkers identifying patients at higher risk of developing severe adverse reactions. This is particularly urgent for patients at risk to develop progressive multifocal leukoencephalopathy (PML) because of natalizumab treatment. In fact, as of the 31st of May 2014, 474 cases of natalizumab-associated PML have been described (http://multiple-sclerosisresearch.blogspot.it/2014/07/clinic-speak-natalizumab-pml-update.html).

The present article reviews some biomarkers that have been proposed to evaluate the safety of natalizumab therapy as well as the most promising results in this field.

2. Known predictive markers for natalizumab-related PML

PML is a demyelinating brain disease caused by the JC virus (JCV) (Brew et al., 2010). JCV infection is frequently acquired during childhood; afterwards, the virus persists in the body in a latent state, replicating at low levels only episodically (Hou and Major, 2000; Khalili et al., 2008). PML, which was initially diagnosed mainly in patients with AIDS or lymphoproliferative disease (Calabrese et al., 2007), is now also observed during therapy with a variety of immunomodulating drugs, natalizumab being the most frequently implicated, especially in patients without an underlying predisposing condition (Carson et al., 2009; Schmedt et al., 2012; Piccinni et al., 2013). As of September 2, 2014, the overall incidence of PML in natalizumab-treated patients is 3.72 per 1000 patients (http://www.biogenidec-international.com/tysabri.aspx?ID=4763; accessed October 24, 2014). While in severely immunosuppressed patients PML is often fatal (Tan and Koralnik, 2010), the disease developing under natalizumab is not always lethal, with an overall mortality of 22% (http://www.biogenidec-international.com/tysabri.aspx?ID=4763; accessed October 24, 2014), mostly due to the PML immune reconstitution inflammatory syndrome (Clifford et al., 2010). The majority of survivors of natalizumab-associated PML are left with a moderate-to-severe disability, depending on the location more than on the size of lesions, the most serious ones being in the brainstem (Clifford et al., 2010).

In MS patients, an early diagnosis of PML in an asymptomatic phase is crucial because it is associated with better clinical outcomes (Wattjes et al., 2014); indeed, the sooner PML is recognized, the therapy stopped, and plasma exchange initiated, the better the outcome (Chalkley and Berger, 2013). However, at present, there is no blood biomarker of JCV activity that can be used alone to diagnose PML, and a failure to detect JCV DNA in the cerebrospinal fluid (CSF) does not rule out the possibility of having PML, particularly in the earlier stages of the disease (Brew et al., 2010; Cordioli et al., 2014). The only humoral parameter obtained routinely is the JCV seropositivity status, which is evaluated by detecting antibodies directed against JCV VP1 (the main surface JCV protein) using the single validated STRATIFY JC virus™ assay (Gorelik et al., 2010; Bozic et al., 2011; Lee et al., 2013).This assay allows neurologists to detect patients at higher risk of developing PML. In particular, three factors—the presence of anti-JCV antibodies, with a lower risk of developing PML in patients with low antibody titers (Plavina et al., 2014), previous use of immunosuppressants, and protracted duration of treatment, especially if longer than 2 years—seem to contribute to the overall risk of natalizumab-associated PML (Bloomgren et al., 2012). Patients with all three risk factors are those at the greatest risk (Sandrock et al., 2011). However, although this risk-factor algorithm may help identifying patients for whom natalizumab is appropriate and may reduce the incidence of PML, its use has some limitations. For instance, because about 57.1% of MS patients are seropositive for JCV (a value very close to the 60% observed in the general population), whereas PML is a rare event, its usefulness in the stratification of patients at risk of PML is limited (Bozic et al., 2011; Lee et al., 2013; Bozic et al., 2014). Furthermore, it appears that the knowledge of these risk factors has not led to a reduction in the incidence of PML in natalizumab-treated patients. Indeed, from April 2010 to February 2014 the incidence of PML has remained essentially unchanged, regardless of natalizumab treatment duration (Cutter and Stüve, 2014; Biogen Idec. https://medinfo.biogenidec.com).

The other strategies commonly used for the diagnosis of natalizumab-induced PML, such as magnetic resonance imaging (MRI) (Vennegoor et al., 2011; Ayzenberg et al., 2012), quantitative polymerase chain reaction (PCR) for detection of JCV DNA in CSF (Kappos et al., 2011; Mentzer et al., 2012; Berger et al., 2013), and JCV antibody index in CSF, which measures intrathecal synthesis of anti-JCV antibodies (Warnke et al., 2014), at present, do not appear to be useful as biomarkers predictive of PML risk prior to therapy initiation.

3. Proposed alternative, immunological markers predictive of natalizumab-related PML

Besides a reduced immune surveillance, other host immune factors and modifications of immune-viral interplay may also play a role in PML development. Viral mutations, facilitating the infection of oligodendroglial cells, together with modifications of the immune system composition, appear to be required for latent JCV to become pathogenic (Weissert, 2011). Indeed, in natalizumab-treated patients, mutations in the coding regions of the viral capsid protein VP1 and in the non-coding control region of the virus (Reid et al., 2011) have been associated with PML. Furthermore, additional secondary effects of natalizumab on immune cells other than its ability to inhibit the crossing of the blood brain barrier have also been documented (Stüve, 2008; Koudriavtseva et al., 2014). Thus, alternative immunological markers helping in the identification of MS patients at risk of PML prior to initiation or during natalizumab therapy could be critical in guiding the decision to start or cease treatment.

This review will focus on analysis performed on peripheral blood samples, as reported below and in Table 1, because central nervous system (CNS) tissue cannot be routinely obtained for diagnostic purposes because of the potential adverse effects. Similarly, CSF, that may reflect cellular events within the parenchyma, although more easily accessible, cannot be considered the ideal biological material for the screening of natalizumab-treated patients at risk of PML.

3.1. Anti-JCV neutralizing activity

Very recently, a lack of a correlation between the level of anti-JCV antibodies and anti-JCV neutralizing activity was demonstrated, suggesting that the serum anti-JCV neutralizing activity could be better correlated to the actual risk of developing PML during natalizumab treatment (Diotti et al., 2014). This may possibly allow an improved risk stratification of natalizumab-treated patients.

3.2. Individual genetic predisposition

The risk of developing PML might critically depend on host genetic factors that establish the immune response to the JCV, and protect from its spread from the peripheral places of persistency or latency to the brain. By determining HLA-alleles with single-nucleotide polymorphism imputation, PCR amplification with sequence-specific primer kits, or with a reverse PCR sequence-specific oligonucleotide method, a strong association between class II gene variants and JCV infection was found in Scandinavian and German patients with MS and in Swedish controls (Sundqvist et al., 2014). In particular, alleles within the HLA-DRB1*15 haplotype appear to be associated with a protective effect