The treatment of multiple sclerosis (MS) has become more complex as the number of disease-modifying therapies (DMTs) for MS with unique immunomodulating properties continues to grow. Clinical trials and postmarketing studies have identified various opportunistic infections in the central nervous system of patients with MS receiving some of these drugs. Progressive multifocal leukoencephalopathy (PML), fungal infections, and herpesvirus infections have all been linked to treatment of MS with certain DMTs. Early recognition, diagnosis, and treatment of these infectious complications are crucial to improve clinical outcomes and avoid their potentially devastating consequences; however, their subtle and uncharacteristic disease presentation makes this goal challenging. This review illuminates some of these challenges and, in particular, the risk stratification, diagnosis, and management of PML in patients receiving natalizumab. The role and safety of vaccines in patients with MS and their potential to interact with certain DMTs also are crucial concerns.

Infectious Complications of Multiple Sclerosis Therapies

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Abstract The treatment of multiple sclerosis (MS) has become more complex as the number of disease-modifying therapies (DMTs) for MS with unique immunomodulating properties continues to grow. Clinical trials and postmarketing studies have identified various opportunistic infections in the central nervous system of patients with MS receiving some of these drugs. Progressive multifocal leukoencephalopathy (PML), fungal infections, and herpesvirus infections have all been linked to treatment of MS with certain DMTs. Early recognition, diagnosis, and treatment of these infectious complications are crucial to improve clinical outcomes and avoid their potentially devastating consequences; however, their subtle and uncharacteristic disease presentation makes this goal challenging. This review illuminates some of these challenges and, in particular, the risk stratification, diagnosis, and management of PML in patients receiving natalizumab. The role and safety of vaccines in patients with MS and their potential to interact with certain DMTs also are crucial concerns.

Treatment paradigms for multiple sclerosis (MS) have become increasingly complex with the advent of new and emerging therapies. There are now several distinct disease-modifying therapies (DMTs) approved by the US Food and Drug Administration (FDA) to treat MS, and many other agents currently are being tested. Clinical trials and postmarketing studies have identified infectious complications associated with certain DMTs, including opportunistic infections involving the brain and spinal cord.

Opportunistic infections are defined as infections caused by pathogens that usually do not cause disease in a host with a healthy immune system. A compromised immune system, however, presents an opportunity for the pathogen to become infectious. Such infections typically result from recrudescence of a previously latent infection acquired earlier in life; perturbation of the immune system by DMTs can increase the risk of pathogenic infections. The development of newer DMTs has introduced new infectious risks that are not typically associated with MS, including fungal and herpesvirus infections. DMT exposure in patients with MS also may increase the risk of autoimmune conditions such as thyroid disease and may alter patient response to vaccinations.

Of most concern in patients with MS receiving DMTs is natalizumab-related progressive multifocal leukoencephalopathy (PML). Treatment of PML involves rapid extraction of natalizumab from the immune system, typically using plasmapheresis.

Infectious complications of current and emerging MS therapies warrant further investigation and consensus building among healthcare providers. Within this context, the role and future direction of vaccination in patients with MS treated with immunomodulatory therapies needs fine-tuning.

This comprehensive review, based upon several reports presented at a symposium held during the joint 28th Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) and the 19th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), will shed light on some of these challenging issues. The panelists included:

- Joseph Berger, MD, Ruth L. Works Professor of Neurology, University of Kentucky Medical Center, Lexington, Kentucky, who spoke on “Opportunistic Infections with Disease-Modifying Drugs”;
- Bruce A. Cohen, MD, Professor, Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, who talked about “Immune Reconstitution Inflammatory Syndrome”;
- Patricia K. Coyle, MD, Professor and Vice Chair, Clinical Affairs, Department of Neurology, and Director, MS Comprehensive Care Center, Stony Brook University Medical Center, Stony Brook, New York, who addressed “Vaccinations in MS”;
- Samuel F. Hunter, MD, PhD, Neuro-Nexus Education Center, Novel Pharmaceuticals Institute, Advanced Neurosciences Institute, Franklin, Tennessee, who discussed “Herpetic and Other Infections with Current and Future DMTs”; and
- Carlo Tornatore, MD, Vice Chairman and Professor of Neurology and Director of the Multiple Sclerosis Center at MedStar Georgetown University Hosp-

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drug increases the risk of opportunistic urinary tract infections, pneumonia, and HSV or VZV infections, particularly in the weeks following its administration.

**Natalizumab**

Natalizumab is a monoclonal antibody that binds to the α4 subunit of α4β1 and α4β7 integrins. Natalizumab is thought to exert its effects in relapsing MS through the α4β1 component, blocking binding to the endothelial receptor vascular cell adhesion molecule 1 (VCAM-1), which attenuates inflammation by preventing the transmigration of lymphocytes across the endothelium into the parenchymal tissue.³

The most worrisome potential adverse effect of natalizumab is PML, a potentially fatal opportunistic infection caused by the neurotropic strain of the John Cunningham polyomavirus (JCV). Specifically, viral proliferation in the central nervous system (CNS) and subsequent infection of oligodendrocytes lead to a serious demyelinating disease of the white matter in patients who are immunocompromised, such as those with Hodgkin's lymphoma or AIDS, or are being treated with immunosuppressive agents. JCV is latent in the kidneys and lymphoid organs of healthy individuals; it is unknown whether it inhabits the CNS of healthy people or immunosuppressed patients without PML.⁶

As of March 31, 2014, approximately 125,800 patients had received natalizumab in the postmarketing setting worldwide. As of May 7, 2014, the overall incidence of PML was 3.610 per 1,000 of these patients; 23% of them died.³ Three identified risk factors that substantially alter an individual's risk of PML include duration of natalizumab treatment, prior history of immunosuppressive therapy, and serum anti-JCV antibody status. The risk for PML may be as high as 1:90 with natalizumab treatment exceeding 24 months, prior use of immunosuppressants, and serum anti-JCV antibody positivity.

**Risk stratification.** One way to stratify PML risk is by treatment duration or epoch. The incidence of PML among patients who received a mean of 17.9 natalizumab infusions was 1.0 per 1,000 treated patients.⁷ In postmarketing stud-
ies, the incidence of PML increased over time, with the risk rising substantially after 24 months of therapy; however, the risk of PML did not continue this upward trend beyond this point. Categorization by treatment epoch (1–12 infusions, 13–24 infusions, 25–36 infusions, etc) clearly showed that PML risk is time-dependent up to a certain point, with a longer duration of therapy associated with an increased risk of infection. For example, the incidence of PML within the first year of natalizumab therapy is only about 0.07 per 1,000 treated patients, but it substantially increases after 25 months of therapy to an average of 1.73 infections per 1,000 treated patients (Figure 1).5

Stratification of PML risk by prior immunosuppressant exposure also is important. The Tysabri Global Observational Program in Safety (TYGRIS) demonstrated that prior immunosuppression in natalizumab-treated patients increased the risk of PML from a mean of 0.88 per 1,000 patients in the first 24 months of treatment to 6.1 per 1,000 patients between 25 and 48 months of exposure.6 A longer washout period between immunosuppressant use and natalizumab therapy did not appear to be associated with a decreased risk of PML.

Prior exposure to JCV apparently is required for PML development. About 35%–80% of adults in the general population have been exposed to JCV; in population-based studies, the exposure rate was about 55%, based upon JCV-antibody testing. A negative JCV-antibody test result, therefore, does not indicate absence of exposure but, rather, a remarkably lower risk of developing PML. Men may have a greater predilection for a positive JCV-antibody response, and the rate of antibody response increases with age.8,9 False-positive test results range from 2.4% to 2.7%; the false-negative rate probably is much higher.

Berger et al10 recently investigated the presence of JCV in blood and urine and the serum JCV-antibody status in 67 patients treated with natalizumab. Approximately 40% of patients were seronegative, but a large proportion (37%) of those testing negative for the antibody had evidence of JCV. Thus, the actual exposure to JCV in this particular cohort of patients was about 75%, as opposed to a presumed 60% who were seropositive for JCV antibody.

The JCV-antibody index may further define PML risk in patients who are seropositive for the JCV antibody (Table 1). JCV-antibody levels are determined using an enzyme-linked immunosorbent assay (ELISA), which yields a JCV-antibody index, an optical-density measurement of antibody level that serves as a corollary of antibody titer. In natalizumab-treated patients with positive JCV-antibody status and no prior use of immunosuppressants, a higher JCV-antibody index correlates with an increased risk of PML.

This finding was substantiated by Plavina and colleagues,10 who used postmarketing data from the AFFIRM and STRATIFY-1 clinical trials of natalizumab in patients with relapsing MS to determine a link between JCV-antibody index findings and later PML development. The JCV-antibody index was significantly higher in the pre-PML group (antibody index, ~ 2.5) than in the non-PML group (antibody index, ~ 1.5). The JCV-antibody index is not a valid indication of PML risk for patients previously exposed to immunosuppressants.

Identification of patients with PML viremia or viruria with seronegative JCV-antibody status in previous studies may cause some unrest among MS healthcare providers who stratify PML risk in their own patients. In this context, important points remain: the risk is very low during the first year of treatment but substantially higher after 2 years of therapy in JCV-antibody-positive patients, and the risk is highest in patients who test positive for JCV antibody; have a history of immunosuppressant use; and have used natalizumab for more than 2 years. Currently, it is recommended that patients who test negative for JCV antibody undergo repeated serology testing every 6 months during natalizumab therapy. An increase in index value over time may indicate increased PML risk. Measurement of JCV DNA in serum is not predictive of PML risk and is not recommended in routine clinical practice.

**Diagnosing PML.** Diagnostic criteria for PML were published in 2013 in a consensus statement from the American Academy of Neurology’s Neuroinfectious Disease Section.11 Clinical manifestations and magnetic resonance imaging (MRI) findings consistent with the diagnosis and not better explained by other neurologic disorders and demonstration of JCV DNA by polymerase chain reaction in the cerebrospinal fluid (CSF) are considered diagnostic. Typical clinical manifestations consist of sensorimotor symptoms, vision abnormalities, dysarthria, cognitive impairment, and behavior changes. MRI features consistent with PML include signal that appears hyperintense on T2/fluid-attenuated inversion recovery sequences and hypointense on T1-weighted sequences, presence of restricted diffusion on diffusion-weighted sequences, gadolinium enhancement, predilection for frontal and parieto-occipital lobes, and absence of mass effect.

**Treatment of PML.** Owing to the serious nature of the disease and the difficulty

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**TABLE 1**

<table>
<thead>
<tr>
<th>JCV Antibody Index</th>
<th>PML Risk/1,000 Anti-JCV Antibody-positive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–24 months</td>
</tr>
<tr>
<td>≤ 0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>≤ 1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>≤ 1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>≤ 1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*JCV = John Cunningham virus

* Patients had no prior immunosuppressant use. Patient numbers in the study were insufficient to calculate risk thresholds below 0.9.

Source: Plavina et al10
of conducting formal controlled trials, treatment options for PML are largely based on anecdotal experience. The current standard of care for PML treatment is accelerated withdrawal of natalizumab from the immune system, typically using plasmapheresis to restore CNS lymphocyte trafficking. However, rapid withdrawal of natalizumab may precipitate immune reconstitution inflammatory syndrome (IRIS), a potentially serious complication with severe morbidity. Other treatment options for PML have been reported to be effective primarily in patients with AIDS, but clinical trial data to establish their true efficacy are not available. Some of these therapies include mirtazapine, mefloquine, cidofovir, and risperidone. Aside from supportive care, the treatment of PML remains a significant challenge.

**IRIS.** Shelburne and colleagues described IRIS as "a process in which clinical deterioration occurs shortly after initiation of HAART [highly active antiretroviral therapy] due to restoration of the capacity to mount an inflammatory immune response to either infectious or noninfectious antigens." A similar process can develop in individuals who are not infected with human immunodeficiency virus (HIV) who undergo reversal of immune suppression and often is seen when natalizumab-treated patients stop taking the drug to combat PML. The demonstration of corresponding inflammatory changes on neuroimaging, often associated with contrast enhancement, is required to make a diagnosis of IRIS. However, it is often difficult to discern such changes due to worsening of PML from those of active MS lesions.

Suspicion of IRIS should be raised if worsening neurologic symptoms emerge weeks to a few months following a stable period after natalizumab withdrawal. Enhancement and enlargement of the PML lesion(s), occasionally associated with focal edema and a mass effect, typically appear on MRI. Nevertheless, there is no definite way to discriminate worsening PML from IRIS on standard MRI alone. Proton magnetic resonance spectroscopy may be valuable in identifying PML-IRIS.

One observational study showed that lesions of patients with PML-IRIS were associated with significantly higher choline-to-creatine (\(P = 0.0001\)), myoinositol-to-creatine (\(P = 0.02\)), lactate/lipid at 1.3 ppm-to-creatine (\(P < 0.0001\)), and lipid at 0.9 ppm-to-creatine (\(P = 0.002\)) ratios, and a significantly lower \(N\)-acetylaspartate-to-creatine ratio (\(P = 0.02\)) compared to lesions of patients without IRIS. Additionally, hyperperfusion assessed by arterial spin-labeling MRI within 3 months of PML onset showed promise in a recent study in predicting the absence of IRIS.

IRIS can occur at the time of PML diagnosis, before natalizumab discontinuation (early PML-IRIS), or following natalizumab withdrawal (late PML-IRIS). Tan and coworkers reported a retrospective review of approximately 40 cases of natalizumab-related PML, classified by early enhancement at diagnosis of PML (n = 17) or the later appearance of enhancing lesions following natalizumab withdrawal (n = 23). The mean duration from plasmapheresis to IRIS was about 2.8 weeks in early PML-IRIS versus 4.3 weeks in late PML-IRIS. No correlation between initial JCV load in the CSF or prior immunosuppressive therapy and mortality was found. Likewise, mortality was comparable between patients with early or late PML-IRIS. Early PML-IRIS was associated with a poorer mean follow-up Expanded Disability Status Scale (EDSS) score (8.7) than late PML-IRIS (7.1), although the difference did not reach statistical significance. Corticosteroid therapy during IRIS was associated with more favorable disability outcomes.

Currently, high-dose methylprednisolone given intravenously for 5 days, followed by a course of oral corticosteroids for 1–3 months, is recommended for IRIS treatment. Corticosteroids diminish specific JCV cytotoxic T-lymphocyte reactivity in the blood, potentially interfering with CNS entry of effector cells necessary to control infection. Because corticosteroids impact the JCV-specific T-lymphocyte response, steroid treatment is not recommended unless there is clinical and radiographic evidence to support IRIS. Other therapies such as maraviroc, mefloquine, thalidomide, and montelukast have shown varied potential effectiveness.

**HSV and VZV infections.** Other natalizumab-related opportunistic infections observed during MS therapy include HSV-1, HSV-2, and VZV infections. Natalizumab inhibits migration of CD4+ T lymphocytes into the CNS, which potentially impairs immune surveillance for these infections. In addition, as demonstrated in a mouse model, CD8+ T lymphocytes may be important for HSV-1 recovery.

A recent study involved data from the FDA’s Adverse Event Reporting System (FAERS) of 20 laboratory-confirmed HSV and VZV infections in the brain and spinal cord associated with natalizumab therapy. Patients had received a median of 21 monthly natalizumab infusions; 10 cases of HSV encephalitis, 5 of HSV meningitis, 2 of VZV meningitis, and 1 each of HSV meningoencephalitis, VZV meningoradiculitis, and VZV meningo-myelitis were described. Seven patients had not used an immunosuppressant previously. Two patients with HSV encephalitis succumbed to their infections. Most surviving patients recovered as of the last follow-up assessment, but four had residual neurologic sequelae, including neuropsychiatric impairments. One patient developed laboratory-confirmed PML following successful treatment of HSV encephalitis.

**Other natalizumab-related infections.** It remains unclear whether accelerated natalizumab withdrawal via plasmapheresis or prophylactic antiviral therapy alters the overall course or prognosis of natalizumab-related herpesvirus infections. However, previous cases demonstrated apparent good response with
early detection and appropriate treatment with antiviral agents, including acyclovir, valacyclovir, and fampciclovir.30

Other postmarketing reports of natalizumab-related infections included CNS toxoplasmosis (one case of encephalitis and one case of ocular infection), Cryptosporidium gastroenteritis, CNS cytomegalovirus, and cryptococcal meningitis in a patient previously treated with mitoxantrone.30

**Fingolimod**

Fingolimod acts by binding to the sphingosine-1-phosphate receptor on lymphocytes, which prevents the egress of lymphocytes from lymph nodes. The sequestration of autoreactive lymphocytes prevents their recirculation into the CNS, thereby inhibiting one of the primary steps in MS pathogenesis. CD4+ and CD8+ effector memory T lymphocytes are spared, which is important for immune surveillance. Lymphocyte sequestration is reversible; lymphocyte counts decrease to 24%–30% of baseline within 2 weeks of fingolimod exposure but return to normal within 6–8 weeks of discontinuation.31-33

The presence of significant lymphopenia (< 200 cells/µL) has raised concern about the increased risk of opportunistic infections, although infection rates associated with fingolimod have been relatively low. Pooled data from three pivotal phase 2 and 3 trials (FREEDOMS, FREEDOMS II, and TRANSFORMS) showed that the overall incidence of infections (including serious infections) among patients with MS treated with 0.5 or 1.25 mg of fingolimod was similar to that among patients receiving placebo or intramuscular [IM] interferon β-1a.34 There was a small increased risk of herpesvirus infections per 100 patient-years among those given 0.5 mg of fingolimod (6.3) or 1.25 mg of the drug (5.9) when compared with patients given placebo (5.7) or IM interferon β-1a (3.0). Likewise, there was a modestly increased risk of VZV infections per 100 patient-years in the groups receiving 0.5 mg and 1.25 mg of fingolimod (1.0 and 1.2, respectively) when compared with the risk in patients receiving placebo (0.5) or IM interferon β-1a (0.2). Of two reported cases of PML in fingolimod-treated patients, one was associated with prior exposure to natalizumab,35 and the other was rediagnosed as neuromyelitis optica. Overall, lymphopenia is not a compelling risk factor for infections.

**Teriflunomide**

Teriflunomide is an active metabolite of leflunomide that impedes the de novo synthesis of pyrimidine nucleotides through inhibition of dihydro-orotase dehydrogenase.36 It hinders T-lymphocyte activation and cytokine production and promotes cytostatic effects on proliferating B and T lymphocytes.37 Pooled data from three phase 2 and 3 (TOWER, TEMSO, TENERE) clinical trials showed no increased rate of infection among teriflunomide-treated patients taking either 7 or 14 mg daily.38-40 Likewise, no deaths from opportunistic infections were reported.38

**Dimethyl Fumarate**

The precise mechanism of action of dimethyl fumarate, a fumaric acid ester, in patients with MS is unknown. It may activate nuclear factor (erythroid-derived 2)-like 2 (Nrf2),41 inhibit adhesion molecule and proinflammatory cytokine expression, decrease circulating T lymphocytes, and promote a shift from Th1 to Th2 cells.42,43 Fumaric acid esters used in Europe to treat psoriasis have shown a relatively favorable safety profile.44 Two cases of PML recently were reported in patients treated with this formulation for 3–5 years.45,46 although one had used immunosuppressants and corticosteroids previously.46 No increased risk of opportunistic infections was noted during pivotal MS trials.

**INVESTIGATIONAL MONOCLONAL ANTIBODIES**

**Rituximab and Other Anti-CD20 Antibodies**

Rituximab is a chimeric monoclonal antibody that targets the CD20 receptor on the surface of B lymphocytes. Rituximab therapy causes rapid depletion of B lymphocytes for 4–12 months,47 with naïve B lymphocytes recovering before memory B lymphocytes. Other anti-CD20 monoclonal antibodies currently in clinical development for use in the treatment of MS include ocrelizumab, ofatumumab, and ocaratuzumab.

Rituximab is associated with an increased risk of PML, reactivation of hepatitis B, and possibly Pneumocystis carinii pneumonia among patients with lymphoma and rheumatoid arthritis. Approximately 80 rituximab-related PML cases have been reported, primarily in patients with chronic lymphocytic leukemia and other lymphoproliferative disorders, which inherently carry an increased risk of PML. Patients treated with rituximab for systemic lupus erythematosus, rheumatoid arthritis, antineutrophil cytoplasmic antibody-positive vasculitis, cryoglobulinemia, and autoimmune thrombocytopenia also have developed PML.48,49

**Alemtuzumab**

Alemtuzumab is an anti-CD52 humanized monoclonal antibody that induces rapid depletion of circulating B and T lymphocytes followed by repopulation, leading to a distinctive lymphocyte profile. In phase 2 and 3 clinical trials, patients treated with 12 or 24 mg/d of alemtuzumab had a higher risk of infection (16%) than did control patients given 44 µg of interferon β-1a subcutaneously 3 times a week (2%-4%). Infections reported in patients taking alemtuzumab were predominantly mild to moderate in severity and consisted mainly of nasopharyngitis, urinary tract infections, upper respiratory tract infections, and herpes viral infections (16% in the alemtuzumab 12-mg and 24-mg groups versus 2%-4% in the subcutaneous interferon β-1a group).50-52 In light of the latter risk, phase 3 clinical trials were amended to include prophylaxis with acyclovir 200 mg twice daily during alemtuzumab administration and for approximately 1 month following treatment.51,52 Serious opportunistic infections in the setting of alemtuzumab-induced lymphopenia were absent in all clinical trials.

**VACCINES**

A vaccine is a biologic preparation that improves immunity to a particular
infectious disease. Inactivated (killed) and activated (live) vaccines elicit an immune response against modified antigens of a specific agent, ultimately leading to a more efficacious immune response during a subsequent exposure to the pathogen. Neurologic complications of vaccinations are rare and often monophasic, and affected patients generally demonstrate good clinical recovery.3-5 Vaccination of immunocompromised patients, including patients with MS being treated with immunomodulatory DMTs, has become controversial. The safety and overall efficacy of vaccinations in MS and whether vaccines cause MS or MS disease activity have been considered.

Several small cohort trials have shown increased relapse rates during “at-risk” periods, defined as 2 weeks before and 5 weeks after the infectious event.4,5 Upper respiratory tract infections, especially those caused by adenoviruses and rhinoviruses, were more common triggers of MS relapses than gastrointestinal infections. Bacterial infections were associated with increased MS disease activity and possibly more severe relapses than viral infections. However, what exactly constituted an “infection” in these studies was not well defined and was often self-diagnosed.

In 2012, the Institute of Medicine (IOM) compiled a comprehensive report of adverse effects related to vaccination use worldwide.6,7 The IOM study examined eight vaccines, including influenza, hepatitis A and B, pertussis/tetanus/diphtheria, mumps/measles/rubella, meningococcal, and human papilloma virus vaccines, for evidence of a causal relationship to MS and other autoimmune conditions. There was no convincing evidence that any of these vaccines caused MS or induced MS relapses, and other reviews reported similar findings.

Owing to the purpose of immunization in preventing communicable infectious diseases, which ultimately may reduce the risk of MS relapses, vaccinations are beneficial as long as they are relatively safe and have no serious side effects. Inactivated vaccines generally are considered safe to use in patients with MS, even during immunomodulatory therapy. However,
Natalizumab-related PML continues to be the infectious complication of greatest concern. Combination approaches to PML treatment have been proposed, but better study protocols are needed to determine effective methods for eradicating JCV from the CNS.

The role and safety of vaccinations in MS have grown increasingly important as new immunomodulating therapies become available. Use of inactivated vaccines in patients with MS is considered safe and generally is recommended in groups of individuals at higher risk of infection. Previously unforeseen infectious complications are a distinct challenge in the care of these patients and require close scrutiny among healthcare providers and their patients.


Inactivity in MS therapy.


THE NEUROLOGY REPORT | Summer 2014 27