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REVIEW ARTICLE

Infection Risk in Patients on Multiple Sclerosis Therapeutics

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Abstract The interface of multiple sclerosis (MS) and infection occurs on several levels. First, infectious disease has been postulated as a potential trigger, if not cause, of MS. Second, exacerbation of MS has been well-documented as a consequence of infection, and, lastly, infectious diseases have been recognized as a complication of the therapies currently employed in the treatment of MS. MS is a disease in which immune dysregulation is a key component. Examination of central nervous system (CNS) tissue of people affected by MS demonstrates immune cell infiltration, activation and inflammation. Therapies that alter the immune response have demonstrated efficacy in reducing relapse rates and evidence of brain inflammation on magnetic resonance imaging (MRI). Despite the altered immune response in MS, there is a lack of evidence that these patients are at increased risk of infectious disease in the absence of treatment or debility. Links between infections and disease-modifying therapies (DMTs) used in MS will be discussed in this review, as well as estimates of occurrence and ways to potentially minimize these risks. We address infection in MS in a comprehensive fashion, including (1) the impact of infections on relapse rates in patients with MS; (2) a review of available infection data from pivotal trials and postmarketing studies for the approved and experimental DMTs, including frequency, types and severity of infections; and (3) relevant risk minimization strategies, particularly as they pertain to progressive multifocal leukoencephalopathy (PML).

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Key Points

Exacerbation of multiple sclerosis (MS) has been well-documented as a consequence of infection.

Infectious diseases have been recognized as a complication of the therapies currently employed in the treatment of MS.

We can characterize and minimize the risk of infection associated with disease-modifying therapies in MS.

1 Introduction

1.1 The Immunological Basis of Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) disease typically characterized by focal neurologic deficits and relapses that can result in disability. Disease-modifying therapies (DMTs) that temper the course of the disorder alter immune function and potentially increase the risk of infection. In this review, we address the impact of infections on relapse rates, the current experience and infectious risks with available MS DMTs and those in development, and the state of knowledge regarding risk minimization strategies with focus on progressive multifocal leukoencephalopathy (PML) and varicella zoster, among infectious concerns. As our knowledge of newer DMTs remains incomplete, careful surveillance for infectious complications is warranted.

A relapse is defined as onset of an acute new focal symptom. The use of relapse rate (relapses/time interval) to evaluate disease activity is an important outcome as relapses are one of the more easily recognized and quantifiable measures of disease, while the predictive value of relapse rate for disease progression remains uncertain [1]. Disease activity can also be followed by magnetic resonance imaging (MRI); in fact, MRI abnormalities have been incorporated into the definition of MS [2]. MRI is used routinely in therapeutic trials and in decision making in clinical care.

Relapses coincide with acute inflammation and evidence of altered or increased immune activity. The pathology of MS is generally characterized by discrete areas of inflammation accompanying demyelination in optic nerves, brain, or spinal cord. The use of DMTs is the standard of care for patients with relapsing forms of MS. DMTs perturb the immune system and changes in relapse rates and patient outcomes with their use the autoimmune hypothesis underlying the pathogenesis of MS. However, the immunological perturbation accompanying their use raises concerns about the potential to predispose to infectious complications.

Pathologic changes in nervous system tissue from MS patients include well-demarcated areas of loss of myelin and inflammatory cell infiltration in and around this tissue. These lesions are often visible and are referred to as 'plaques'. Given the pathology, immune reactions that result in destruction of myelin have been the focus of the bulk of investigations and theories about causation of this disease [3]. The inflammatory infiltrate consists of both T cells (CD8+ and CD4+) and macrophages. The inflammatory pathology of MS suggests a T cell plus macrophage or antibody plus complement attack on myelin and underlying axons [4]. Glial cells, specifically microglia and astrocytes, can induce, regulate, and are themselves regulated by, inflammatory immune responses within the CNS. Inflammatory cell recruitment to MS lesions is associated with certain cytokines and with the upregulation of various leukocyte adhesion molecules on endothelial cells (for an expanded discussion see Sospedra and Martin [5]). Entry of T cells to the CNS involves 'crossing the blood–brain barrier' (BBB). Access of leukocytes is controlled via complex interactions with glial components of the BBB which include receptors on astrocytes and immunoregulatory mediators such as interferons (IFNs) that regulate cellular traffic. Myeloid cells at the BBB present antigen to T cells and influence cytokine effector function. Myelin-specific T cells interact with microglia and promote differentiation of oligodendrocyte precursor cells in response to axonal injury [6]. It should also be mentioned that the presence of B cells in MS plaques has been well-described [7], and they too are believed to play a role in the pathology of the disease [8]. Ongoing degeneration and loss of CNS tissue may occur independent of, or in combination with, demyelination and the florid plaques or lesions that have long been considered the pathologic underpinning of MS. Some investigators have suggested that the development of MS-like lesions requires factors beyond cell-mediated immunity [9]. Still, inflammation and immune activity remain central to understanding of the disease process, and described responses of the adaptive immune system offer targets for immunomodulatory therapies that are currently used for MS.

The presence of microglia cells with altered morphology in the brain implies inflammation. It is clear that the molecular expression profile that accompanies an activated microglial cell is influenced by factors both intrinsic and extrinsic to the brain. Central inflammation may be modulated by peripheral inflammation, and it is understood that peripherally-induced cytokines, e.g. interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 and type I IFNs (IFNα and IFNβ), can initiate synthesis of cytokines and inflammation in the CNS. Injury signals can reach the brain and initiate changes through blood-borne mediators that cross the BBB at anatomically sensitive sites [10]. Because systemic inflammatory stimuli that circulate in the blood may get into the CNS and induce changes, it is understood that circulating cytokines and other inflammatory molecules from systemic infections can affect the brain [3].

1.2 Infectious Disease and the Course of MS

In addressing the topic of infections and their effect on MS relapses, it is important to consider the concept of pseudo-exacerbation, or worsening of symptoms in MS that are associated with, if not attributable to, concurrent fever or illness. While the line between pseudo-exacerbation and new disease or relapse is not always clear, the definition of relapse typically includes absence of either fever or infection. Therefore, screening processes, including history, physical examination, and urinalysis, are often employed when deciding whether new complaints are due to other illness or MS itself. This is practical for two reasons.

First, treating an infection that results in pseudo-exacerbation may alleviate the neurological complaint. Second, as high-dose corticosteroids are generally administered for an acute relapse, it avoids the potential risk of aggravating a pre-existing infectious illness. Concurrently, there are concerns that infections may actually lead to new or worsened disease.

Several observational studies have addressed the issue of infections and risk of relapse in MS by comparing the rate of relapse during 'risk' periods against control periods. In the pioneer study by Sibley et al. [11], risk periods were defined to include the 2 weeks prior to infection and

5 weeks after infection, and the rate of relapses during the at-risk period was reported as 2.8-fold higher. This study followed 170 patients with clinically definite MS who were assessed for infections and relapses at monthly intervals for a mean of over 5 years. In a similar parallel study, 660 patients with MS were followed for just over 2 years, and the relative risk of relapses was found to be only 1.3-fold the control periods when using an at-risk time period of 4 weeks [12]; however, no significant association between MS relapse and infection was observed when using the 7-week time window of the previously published study [11]. In a subsequent study, 73 patients with MS were enrolled in a prospective survey with clinical assessments at 8-week intervals for an average of 1.7 years [13]. For confirmed infections, three serial MRI examinations at 3-week intervals were arranged. A total of 167 infections and 145 relapses were recorded, and analysis was performed on the 7-week risk period previously defined [11] to compare risk and control periods, yielding a relapse rate ratio of 2.1. However, MRI results in this study were puzzling; in comparing the three serial scans performed following any confirmed infection, the percentage of active scans and the mean number of enhancing lesions per scan remained unchanged. The report of increased risk of relapse associated with infection in this later study could be criticized if one believes that MRI is a more accurate measure of relapse than clinical evaluation, as pointed out in a review of the work by Confavreux [14]. In the study by Buljevac et al. [13], we might also note that when the authors selected a risk period that did not overlap the infection, no significant association was observed between infection and relapse. Although the authors of the study tried to exclude fever-related neurological episodes from their definition of relapse, it is plausible that infection results in "apparent increase of relapse through pseudo-relapses related to fever or transient cytokine modifications" [15].

A more recent article [16] followed 60 patients with MS for infection symptoms and relapses with performance of MRIs on initial visit, and 2 and 12 weeks later, while collecting blood samples at first infection symptom and at 2, 5, 12, and 24 weeks to look at production of cytokines (including IFNγ) and immune activity. The authors reported significant association between systemic infections and risk of MS relapse, increased MRI activity, and T-cell activation. However, we cannot help but wonder about pseudo-exacerbation in this type of study—would association between infections and relapses be found when considering only relapses with new neurological manifestations with respect to the patient's history, noting that relapse with not-before-experienced symptomatology may be more likely to represent true relapse, attack, or actual flare of disease (as noted in the review by Confavreux [14])? In the end, peripheral infectious agents can certainly aggravate the symptomatology of the disease and may increase the risk of relapses and possible infections; the treatment thereof should be adequately assessed and addressed in MS patients in order to improve quality of life, if not progression of the disease.

Whether or not infections are a risk factor for true relapses versus being more likely to result in pseudo-exacerbation, there is agreement that they can lead to the worsening of clinical symptoms. Reports that MS, or symptoms thereof, can flare after infection is supported by evidence that peripheral stimuli can trigger secretion of pro-inflammatory molecules in the brain. A biological explanation for the association between infections and attacks in MS is that "induction by infectious agents of the secretion of pro-inflammatory cytokines such as IFNγ and interaction of the host immune system with viral antigens can result in immune activation leading to relapses" [14]. Although relapsing and remitting episodes remain largely unpredictable, and peripheral infections may or may not be causal, attacks do seem to be related to the presence of measurable peripheral inflammation. In multiple studies, patients with MS have shown increased serum levels of IL-1β, IL-2, IL-4, IL-12p70, IFNγ and TNFα during relapses [17–19]. The number of IL-1β, IL-6 and TNFα secreting cells has been observed to be higher in MS patients during exacerbations [20], and levels of T helper (Th) 17 and regulatory T (Treg) cells in the periphery may be higher in MS patients undergoing a relapse [17]. Also, the cerebrospinal fluid (CSF) cytokine profile can change during relapses, with upregulation of IL-1β, TNFα, and transforming growth factor (TGF)-β, and downregulation of IL-10 [17, 21].

1.3 The Risk of Infection with Disease-Modifying Therapies (DMTs)

With regard to the use of MS therapeutics, markers of inflammation and immune activity have been studied and targeted with great benefit. Interferon-beta (IFN-β) reduces the production of pro-inflammatory cytokines and induces the expression of anti-inflammatory molecules, while glatiramer acetate switches the cytokine profile to a regulatory type, by increasing expression of IL-4, IL-10 and transforming growth factor beta (TGF-β), and by decreasing TNF-α [22]. Monoclonal antibodies (natalizumab and alemtuzumab among others) inhibit leukocyte migration across the BBB [23–25]. Fingolimod interferes with T-cell trafficking, although it may not significantly interfere with function [26, 27]. Dimethyl fumarate, teriflunomide, and others may decrease inflammation either by reducing the number of immune cells or shifting the pro-inflammatory profile to an anti-inflammatory profile [23, 25, 28–31].

A delicate balance between pro- and anti-inflammatory processes exists. For example, treatment of MS patients with TNFα inhibitors has resulted in exacerbation of the disease despite a clear association between TNFα increase and relapses (reviewed by Perry et al. [32]). The link between natalizumab use and complications of PML has shown that CNS leukocyte infiltration may be essential for viral immunosurveillance [33, 34]. In the interesting story of helminth therapy, infection with these worms in the treatment of MS was associated with the induction of CD4+ and CD25+ T cells secreting IL-10 and TGFβ [35]. In addition, the entrance of anti-inflammatory Th2 lymphocytes may contribute to CNS repair in MS [36].

The balance between pro- and anti-inflammatory mechanisms has represented an important issue in MS drug design. Perhaps not entirely unexpectedly, infections have been recognized or associated with the use of some of the drugs used in the treatment of MS. Our understanding of the potential adverse effects of these immunologically active therapies is part of the decision-making process when weighing different treatment options.

With the exception of adrenocorticotropic hormone (ACTH) and corticosteroid therapy, treatments that did not decrease the risk of relapse or alter the course of the disease, no treatments were available for MS until IFN-β1b in 1992. Noting use of IFNs and glatiramer acetate were the primary options for treatment of MS, infectious disease was not a significant concern with DMTs until 2005, when PML was reported as a complication of natalizumab for the first time. In the absence of a neurological debility caused by the disorder that would predispose to infection, such as urinary tract infection with poor bladder emptying or pneumonia from aspiration or impaired clearance of respiratory secretions, MS in the absence of immunomodulatory therapy has not been associated with an increased risk of infection. With time and with the release of newer agents, including other biological agents, the concern about infectious disease as a complication of MS therapy has heightened.

Many of the therapies employed in the treatment of MS have been referred to as neuroimmunomodulators. This term is somewhat misleading. First, the effect of these agents is systemic and not limited to the nervous system. Second, despite seemingly highly-focused perturbations in immune function by design, other downstream effects can result in potentially significant impairment in fighting microbial infection, noting some treatments have proven to be more broadly immunosuppressive than otherwise anticipated. We will next focus on our current state of knowledge regarding available disease-modifying agents and the infectious complications, real and potential, that may be associated with these agents. These infections may be non-opportunistic or opportunistic in nature. The latter result from microorganisms that do not ordinarily cause disease in the presence of normal immune function, but do so only in the setting of immunologic impairment.

1.3.1 Corticosteroids

Corticosteroid therapies (including the use of ACTH, a glucocorticoid receptor agonist) have been employed in the treatment of MS for over 40 years. The purpose of corticosteroids in MS is usually to try and accelerate recovery from an acute relapse; in these instances, treatment duration is short, with little concern for suppressing immune function in a significant way. The use of pulsed corticosteroids administered at monthly or less frequent intervals similarly presents little risk for infection, although more frequent corticosteroid administration may present increasing risk of complications. Glucocorticoids have a broad range of effects on the immune system; they inhibit the production of certain inflammatory mediators, including the cytokines IL-1, IL-6 and TNFα, they reduce macrophage motility and response to IFNγ, and they also downregulate adhesion molecules, inhibit IgE-dependent degranulation and induce eosinophil apoptosis [36]. While glucocorticoids are regarded as more anti-inflammatory than immunosuppressive, they can increase the risk of viral, bacterial, fungal and parasitic infections when used over long periods of time [37]. Infections with *Listeria monocytogenes*, *Mycobacteria tuberculosis* [38], herpes viruses (*Herpes simplex* and *Varicella zoster* viruses), fungal disease and certain parasites are all increased with chronic use, while pyogenic bacteria are the most common pathogens observed with glucocorticoid administration [39]. Vigilance and screening for pre-existing infections is critical prior to or during administration of corticosteroids.

There may be reason to exercise caution before using corticosteroids in conjunction with certain disease-modifying therapies and worsening symptoms, particularly those that may be viewed as 'immunosuppressive' and/or have been associated with the incidence of PML (such as natalizumab). Masking of clinical signs of infection or the exacerbation of latent infection has been known for years as a potential consequence of corticosteroids [40, 41], and potentially serious infections have become more of a risk over time as our armamentarium of drugs has expanded. PML can lead to death if not properly recognized and treated by removing agents that may lower the body's ability to keep the causative John Cunningham (JC) virus at bay, and corticosteroids may inhibit this, although they are an important therapeutic agent in the setting of a complication referred to as PML-immune reconstitution inflammatory syndrome (PML-IRIS). Except under special circumstances, avoiding the use of corticosteroids with infections, including herpetic infections, is warranted.

2 Platform Therapies for MS

Although the use of corticosteroids preceded the era of injectable therapies for MS, the 'platform Therapies', including the various interferon (IFN) formulations and glatiramer acetate, have now been available for more than two decades. We do not have a concern that these drugs predispose patients to infections. Many consider these injectable drugs as first-line and refer to the newer agents as second-line therapies, perhaps suggesting the latter should be reserved for special circumstances. Widespread use of IFN-β and glatiramer, as well as years of experience with these drugs, proves that they do not alter the immune system in ways that suppress the body's ability to fight off infections, respond to vaccinations, or otherwise function. Apart from local infections and rare abscess formation in the context of subcutaneous or intramuscular application complications, the platform therapies are considered safe with respect to infectious side effects, and no increased systemic risk of infection has been found [42–44].

2.1 Interferon (IFN)-β

The first truly effective agent to reduce relapses and new lesion formation was IFN-β-1b. IFN-β-1a and 1b preparations are used in the treatment of MS and applied via intramuscular or subcutaneous injection. IFN-β is involved in the immune response to viral infections and is upregulated during the course of viral illness. The precise mechanisms by which IFN-β-1b (including Betaseron® and Extavia®) and the related compounds IFN-β-1a (Avonex®, Rebif®, and Plegridy™) affect the immune system and MS remains uncertain; however, research shows that these compounds may inhibit T-cell proliferation, increase suppressor T-cell activity, inhibit proinflammatory cytokines such as TNFα and IFNγ, induce immunomodulatory cytokines IL-10 and TGFβ, reduce expression of human leukocyte antigen (HLA) class II and adhesion molecules, block metalloproteinases and chemokines, and/or reduce BBB permeability [45]. Despite possible development of leukocytopenia, abundant data from clinical trials and postmarketing experience indicate that severe infection associated with the use of these agents is exceedingly rare. Although local infections at the injection sites, and even formation of abscesses, have been documented during treatment, the published literature regarding the IFN-βs indicate that there is no increased risk of infection associated with their use.

2.2 Glatiramer Acetate

The second class of therapy developed to treat MS was glatiramer acetate (Copaxone®). This compound is a mixture of synthesized polypeptides with an immunomodulating effect that is injected subcutaneously. The chemical structure is similar to myelin basic protein, a component of myelin, and glatiramer binds various HLA haplotypes of antigen-presenting cells [46]. During treatment, a shift from Th1 to Th2 cells occurs, and this shift leads to increased production of anti-inflammatory cytokines such as IL-4, IL-6, IL-10 and neurotrophic factors [47]. Glatiramer acetate also reduces the release of proinflammatory cytokines such as IL-12, promotes regulatory CD8 cells and the conversion of CD4+CD25 T cells to regulatory CD4+CD25+ T cells [48]. Leukocytopenia and leukocytosis, as well as abnormal lymphocyte morphology, have been reported with the use of glatiramer acetate but no risk of serious infection has been recognized. In phase III trials, local reactions at injection sites were noted, and inflammation as a sign of infectious complications was observed in 27 % of treated patients versus 6 % of placebo-treated patients [49]. However, in follow-up studies since the initial clinical trials, local injection site reactions have been recognized as mild, short-lived, and not necessarily infectious, with no instances of skin necrosis [50].

3 Other DMTs

3.1 Mitoxantrone

Mitoxantrone (or Novantrone®) is a synthetic antineoplastic cytotoxic drug administered via infusion. This is a powerful agent, capable of broad immunosuppression, active both on proliferating and non-proliferative cells. Mitoxantrone, previously used in leukemia, provided another option when it was approved for use as an alternative to the injectable, or platform therapies in 1996. It operates independently of the cell cycle, and its effect on B and T lymphocytes can alter the disease course of MS [51]. Mitoxantrone causes cross-linkage and strand breaks of DNA by intercalation and it has an antiproliferative effect on B and T lymphocytes as well as macrophages.

The most serious risks of the drug are dose-dependent cardiotoxicity and leukemia, whose incidence in practice has appeared to be higher than previously reported in trials [52]. Combined with the introduction of other therapies, concerns about the potential for complications associated with mitoxantrone have increasingly limited the use of this drug over the course of time [51]. In clinical trials, mildly increased numbers of urinary and respiratory tract infections were encountered in treatment groups [53–55]. Theoretically, increased risk of infection could be more concerning in the long-term, although the way in which it is, and has been, employed with time-limited dosing may counteract this.

3.2 Natalizumab

Natalizumab is a humanized monoclonal immunoglobulin (Ig) G4 antibody administered intravenously on a monthly basis that inhibits α-4-integrin and reduces the migration of very late antigen (VLA)-4-positive lymphocytes to the CNS [56].

Natalizumab, marketed as Tysabri®, has demonstrated a robust effect on MS relapse rate and MRI activity. In initial studies for MS, there were frequent reports of infections of the urinary tract and rhinopharyngitis, along with one reported case of fatal herpes encephalitis. Patients treated with natalizumab monotherapy compared with placebo reported incidences of urinary tract infections (21 vs. 17 %), lower respiratory tract infections (7 vs. 16 %), gastroenteritis (1 vs. 9 %), tooth infections (9 vs. 7 %), herpes (8 vs. 7 %), and tonsillitis infections (7 vs. 5 %) [57]. Shortly after the drug's approval for use in both diseases, PML was reported to be associated with natalizumab treatment for Crohn's disease and MS [58–60]. As of November 2014, 517 cases (514 associated with MS and 3 with Crohns disease) of natalizumab-associated PML had been reported [57]. Prior to the observation of natalizumab-associated PML, the disorder was most frequently seen with HIV/AIDS and lymphoproliferative disorders, particularly B-cell malignancies.

The cardinal feature of PML is demyelination, and the myelin loss can be extensive. The disease is often marked by cognitive and behavioral changes, language disturbances, weakness, or visual deficits [61, 62]. Lesions may occur in any location in the white matter [63], thus clinical features are diverse. The gold standard for diagnosing PML is demonstration of characteristic histopathologic changes in tissue coupled with evidence of the virus by electron microscopy or immunocytochemical studies, but diagnosis is most often established in vivo with (1) a compatible clinical picture; (2) a typical brain MRI; and (3) polymerase chain reaction (PCR) detection of the JC virus in the CSF [64]. To date, no treatment has been convincingly effective. The causative agent of PML is a ubiquitous polyoma virus, known as the JC virus, which causes no recognizable clinical illness at the time of initial infection; therefore, the mechanism by which one is infected and the timing of infection remain unknown. Antibodies against the JC virus are not protective against PML and the virus is widespread in the human population, yet only a vanishingly small number of infected persons develop PML. Disorders of cell-mediated immunity increase risk, particularly HIV infection, while restoration of the immune system can arrest PML [65]. PML has been observed with the use of other biologic agents [34], including other monoclonal antibodies such as efalizumab [66], belatacept [67], rituximab [68], infliximab [69] and alemtuzumab [70], but also immunomodulatory agents that are not monoclonal antibodies, such as mycophenolate mofetil [71], fludarabine [72–75], leflunomide [76, 77], and fumaric acid esters [78–80]. However, the risk with these agents is substantially less than that with natalizumab and efalizumab, the latter a monoclonal antibody formerly used in the treatment of psoriasis. Unlike natalizumab, many of the drugs predisposing to PML are used in conditions that already carry a significant baseline risk for PML. Furthermore, the observation that PML does not appear to develop immediately following the introduction of natalizumab suggests that evolution of PML is due to more than simply impaired CNS immunosurveillance. This contrasts with the use of drugs in which PML may occur shortly after their introduction. It is quite possible that a short interval from drug administration to PML indicates that affected individuals were on the precipice of PML and were 'tipped over by the drug' following their introduction [65]. The observation of PML with the use of biologic agents in diseases that may not be illnesses which necessarily predispose to the development of PML by themselves warrants significant consideration in a risk–benefit analysis of therapy.

The mortality of natalizumab-associated PML is approximately 25 % [57], a significantly greater survival rate than in other cases. The earlier that PML is diagnosed, natalizumab discontinued, and plasma exchange initiated, the better the prognosis. Among the survivor cohort of natalizumab-associated PML, most are left moderately to severely disabled [57]. The majority of patients with natalizumab-associated PML also experience PML-IRIS [57]. By definition, IRIS is worsening of symptoms and/or radiographic manifestations in the setting of infection that occurs upon recovery of a suppressed immune system. It was first recognized in patients with AIDS, paradoxically coinciding with the start of antiretroviral therapy and both a decline in HIV viral load as well as improvement in CD4 T-lymphocyte counts. The reversal of immunosuppression with highly active antiretroviral therapy (HAART) in HIV-associated PML has its parallel with the discontinuation of natalizumab (typically combined with initiation of plasma exchange) in natalizumab-associated PML. Survival appears to be better in natalizumab-associated PML-IRIS patients treated with corticosteroids, but while the consensus of expert opinion favors their use, this strategy is not without potential risk in the setting of infection.

The precise explanation for the risk of PML associated with natalizumab is not clear, although decreased immunosurveillance is most often cited. Prevention of the entry of JC virus cytotoxic lymphocytes into the CNS and reduction of antigen-presenting cells may result in predisposition. The release of CD19+ CD10+ pre-B cells that occurs after administration of the drug, cells which can be latently infected with JC virus, may also be important [81].

Use of immunosuppressive therapy prior to natalizumab, including mitoxantrone, methotrexate, and azathioprine, appears to also significantly increase the risk of subsequent development of PML [57]. It has been recommended that all immunomodulatory agents should be discontinued at least 3 months prior to the initiation of natalizumab [82], while washout periods have more of a theoretical than proven benefit in doing anything but perhaps making it more clear that any subsequent development of PML could be attributed, at least mostly, to natalizumab. Importantly, three risk factors have been associated with an increased likelihood of developing PML with natalizumab. These include the presence of JC virus seropositivity, longer duration of natalizumab therapy (especially greater than 24 months), and prior treatment with immunosuppressive therapies [83]. These observations have permitted a rational approach to risk mitigation.

While perhaps the most publicized, PML is not the only postmarket launch infectious complication to have been reported with the use of natalizumab. Specifically, there have been well-documented reports of associated herpetic and varicella complications. A review of some 20 cases of such herpes and/or varicella cases associated with natalizumab use was published in 2013 [84]. The authors searched the US FDA Adverse Event Reporting System (FAERS) and MEDLINE to identify infections that were laboratory confirmed by PCR of the CSF for herpes simplex virus or varicella zoster virus, noting reports of varicella zoster virus myelitis [85–87], herpes simplex encephalitis [88], herpes simplex virus meningitis [89], and zoster [90]. Of the 20 patients, seven received prior immunosuppressives, seven did not receive immunosuppressives, and data were missing for the remaining six patients. Patients received a median of 21 monthly doses of natalizumab prior to presentation. Despite these case reports and case series, an increased risk of serious herpes infections with natalizumab remains to be convincingly established.

3.3 Rituximab

Rituximab is an anti-CD20 monoclonal antibody that targets lymphocytes to deplete B and pre-B cells that express CD20. It is approved for use in the treatment of lymphoproliferative disorders and autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Rituximab is sometimes used off-label in MS-spectrum disorders, noting case series and a phase II study using a single course of rituximab that reduced MRI lesions and rate of relapses over a period of 48 weeks compared with placebo [91]. The incidence of any infection with rituximab was similar in the placebo group (71.4 %) and the rituximab group (69.6 %) in this study. The most common infections (occurring in $\geq$10 % of patients) in the rituximab group were nasopharyngitis, upper respiratory tract infections, urinary tract infections, and sinusitis. Urinary tract infections were more common among patients who received rituximab than among patients who received placebo (14.5 % of the rituximab group vs. 8.6 % of the placebo group), as was sinusitis (13.0 vs. 8.6 %). No clinically significant opportunistic infections were reported. Infection-associated serious adverse events were reported in 5.7 % of patients in the placebo group and 2.9 % of patients in the rituximab group. Of the two serious infection-related adverse events (gastroenteritis and bronchitis) in the rituximab group, both resolved without sequelae. In a primary progressive MS trial, 4.5 % of patients treated with rituximab were found to have severe infections compared with less than 1 % in the placebo arm [92]. Serious complications of this therapy outside of these trials have included manifestation of other viral disease, such as reactivation of hepatitis B, in addition to PML [93, 94]. With rituximab use, immature B cells predominate and this may contribute to transactivation and expression of a neurotropic strain of JC virus; additionally, some effect on T-cell function may result from the drug and this could also play a role in the development of PML [81]. Unlike natalizumab, estimating the risk of PML with rituximab is more difficult as PML has been linked to illnesses for which it is used. Patients identified with rituximab-associated PML often have underlying immune abnormalities related to their primary disorder or secondary to use of other immunosuppressants [95]. From 1997 to 2008, fifty-two patients with lymphoproliferative disorders (generally B-cell malignancies), two with SLE, one with RA, and one with autoimmune pancytopenia were catalogued to have developed PML after rituximab therapy—all had been treated with other immunosuppressive regimens, including hematopoietic stem cell transplantation in seven patients [96]. More recent figures from Genentech indicate that approximately 2 million doses of rituximab have been administered to 1 million patients, among whom 157 cases of PML have been observed (137 with lymphoproliferative disorders, six with RA, eight with SLE and six with AIDS); no known cases have been reported with the use of rituximab in MS or other neurological disorders [97].

While the incidence of PML with rituximab is considerably lower than that with natalizumab, the case fatality rate with rituximab-associated PML is between 90 and 100 % in those diagnosed with PML within 3 months of their last dose [96]. This high rate is explained by the nature of the underlying disorder perhaps coupled by the irreversible nature of the immune abnormalities induced by the drug. It is possible that the number of cases of PML reported with rituximab is an underestimate of the true incidence, while it has yet to be reported in the treatment of demyelinating disease or other neurological disorders. The

risk of PML with anti-CD20 monoclonal antibodies is likely to remain considerably lower than with natalizumab, and to date, no cases of PML have been reported in the treatment of MS or other demyelinating disorder with anti-CD20 monoclonal antibodies. Ocrelizumab studies are also currently ongoing, noting that this is a medication with similarities to rituximab. There are a number of other anti-CD20 antibodies in various stages of development for the treatment of MS, including ofatumumab, in addition to ocrelizumab. It is anticipated that the experience regarding infectious complications with these agents may parallel the experience with rituximab.

3.4 Alemtuzumab

Alemtuzumab (or Lemtrada™) has also been studied for the treatment of MS [98], and was recently approved in the US after first coming on the market in Europe; the delay was at least partly due to safety concerns, which included a significant incidence of autoimmune thyroid disorders and the need for surveillance of blood counts and infection. Alemtuzumab has been administered intravenously in annual therapeutic cycles for MS. Alemtuzumab causes a profound reduction of B and T lymphocytes, and while B cells recover within 3 months, T lymphocytes may remain depleted for more than 5 years [99].

From alemtuzumab studies in MS, infection concerns involved mainly the upper respiratory tract, the urinary tract and herpes. During a comparison study, infections appeared more frequently with alemtuzumab than with IFN-β-1a and, of these infections, 98 % were graded as mild to moderate, while none led to discontinuation of therapy [100]. A similar study revealed infections in 77 % of patients in the alemtuzumab arm compared with 66 % in the IFN arm, with reported incidences of rhinopharyngitis (29 vs. 24 % of patients), urinary tract infections (21 vs. 11 %), and infections of the upper respiratory tract (16 vs. 12 %) [101]. Severe infections were reported in 4 and 1 % of patients, respectively, with reports of mucocutaneous herpes simplex, candidiasis and varicella zoster infections requiring in-patient treatment. Of note, patients treated prophylactically with the antiviral acyclovir resulted in a reduced number of herpes virus infections compared with patients without prophylactic treatment (1 vs. 3 %; then 0.5 vs. 2.8 % after the first alemtuzumab application, and 0.4 vs. 2.1 % after the second alemtuzumab dose)—contributing to recomendation to use prophylactic anti-herpetic therapy for at least two months with administration of alemtuzumab [102].

One patient from an endemic region developed tuberculosis (TB) during alemtuzumab high-dose treatment, resulting in termination of alemtuzumab, and one other patient had to be treated due to a positive tuberculin skin test; both patients responded to anti-TB drugs. PML has been observed with alemtuzumab, including two cases in patients with chronic lymphocytic leukemia and one in a lung transplant recipient [70, 103]. As with rituximab, these cases represent PML in the background of malignancy or severe immunosuppression with co-administration of other immunosuppressants. Despite marked lymphopenia with this agent that effectively removes CD4 and CD8 lymphocytes for long periods of time but permits the recovery of B cells within months of administration, the relative rarity of complications is striking. Even with observed immunological changes, opportunistic infections appear to be very rare with alemtuzumab use in MS, and to date no cases of PML have been reported in MS patients treated with this therapy [81].

4 Oral DMTs for MS

In the past few years, three additional therapies have been approved for use in MS, including fingolimod, teriflunomide, and dimethyl fumarate. These are all medications administered in pill form. When compared with the paucity of complications encountered with long-term use of the injectable 'platform therapies' for MS, there have been some safety concerns with these newer agents. Similar to the intravenous therapies discussed, robust reduction in relapse rates and/or MRI data of newer drugs in trials may be tempered by concerns of infectious and other risks, as well as some uncertainty given less experience with the newer therapies in MS. However, it is interesting to note that all three of the currently approved oral therapies are closely related to drugs previously used in other diseases, in essence providing additional information that can be drawn upon for inference regarding infectious disease risk.

4.1 Fingolimod

The first oral therapeutic agent approved for use in MS was fingolimod (Gilenya®), which is licensed as a first-line therapy in the US and as a second-line therapy in Europe. Initially studied for use in kidney transplant patients, the drug is an antagonist of sphingosine-1-phosphate (S1P) receptors on lymphocytes that modulates their migration from lymphatic tissues [104]. Significant lymphophenia can develop with use but there is an unclear relationship of this to infections, and it has been asserted that immune function remains largely intact despite decreased measurable white blood cell counts. The drug may have the ability to cross the BBB and act in the CNS [105], and it has an effect on S1P receptors in other organ systems, including the heart, lung, and eye, which contributes to monitoring and screening recommendations.

In licensing studies that showed benefit in MS, acute infections of the lower respiratory tract and urinary tract occurred more frequently in patients treated with fingolimod, while severe infections were found in 2–6 % of patients, including a fatal case each of herpes simplex virus encephalitis and disseminated varicella zoster virus infection [106, 107]. An additional patient developed primary varicella zoster virus infection in the extension arm of the TRANSFORMS study [108]. In the FREEDOMS phase III study (n = 1,272), the proportion of patients with any herpes infection was 7.9 % when receiving placebo, 8.7 % when receiving fingolimod 0.5 mg, and 5.8 % when receiving fingolimod 1.25 mg. For herpes zoster, these proportions were 1.0, 1.6 and 0.7 %, respectively, and for serious herpes infections the proportions were 0, 0.2 and 0.2 % [109]. Among 2,315 patients from one phase II trial [110] and two phase III trials [111], 12 of 48 patients with serious infection had herpes virus infection, which included ophthalmic herpes zoster (n = 3), disseminated herpes zoster (n = 2), herpes zoster not otherwise specified (n = 4), herpes encephalitis (n = 1), genital herpes (n = 1) and herpes virus infection not otherwise specified (n = 1) [112].

Anecdotal reports of recurrent zoster and varicella zoster virus encephalitis and vasculitis also appear in the literature [113, 114]. A somewhat difficult-to-interpret risk that has come to light in this new era of therapeutics involves switching among therapies with different associated infectious side effect profiles, including treating patients after use of natalizumab, which is often discontinued due to potential concerns for risk of PML. To date, there have been up to 11 case reports of PML in patients treated with fingolimod post-natalizumab [115]. More recently, a case of PML in MS patient treated with fingolimod has come to light, raising question about risk attributed primarily to this agent [116]. Additionally, there is report of at least one case of PML in a patient treated for demyelinating disorder with fingolimod who did not receive prior natalizumab, in whom retrospective diagnosis of neuromyelitis optica versus multiple sclerosis has been suggested [115].

4.2 Teriflunomide

The second oral agent to become available for the treatment of MS was teriflunomide (Aubagio®), licensed by the US FDA in 2012 and the European Medicines Agency (EMA) in March 2013. Teriflunomide is the active metabolite of leflunomide, which has been used for a number of years in the treatment of RA. The drug acts as a dihydroorotate dehydrogenase inhibitor that limits pyrimidine synthesis in rapidly proliferating cells, blocking activation and proliferation of T and B lymphocytes [117]. In a phase III study of teriflunomide, a minority of patients experienced serious side effects, while a reduction in annual relapse rate, MRI T2 lesion volume and progression of disease were observed [118]. The frequency of serious infections was comparable in all three arms of the study (teriflunomide 7 mg, 1.6 %; teriflunomide 14 mg, 2.5 %; and placebo, 2.2 %). Among these, three cases of pyelonephritis were observed in the 14 mg group and one case of serious herpes zoster infection was observed in the placebo group, but no opportunistic infections were observed. Influenza infections were documented in 9.2 and 12 % of patients in the teriflunomide groups, respectively, versus 10 % of patients in the placebo group, while urinary tract infections were documented in 7.3 and 10.3 % of patients in the drug group versus 9.7 % of patients in the placebo cohort.

Cases of pulmonary TB, *Pneumocystis jieroveci* pneumonia and other pulmonary infections have been reported with leflunomide [119], as have rare reports of PML. The former has resulted in the recommendation to check an individual's TB status, typically by purified protein derivative (PPD) or quantiferon testing, prior to initiation of therapy. Positive findings could warrant further evaluation, and TB, including latent disease, is a contraindication to initiating teriflunomide. A case of PML in a 55-year-old patient with SLE receiving leflunomide has been reported, noting this patient had been previously treated with various other immunosuppressant drugs (prednisone, azathioprine, chloroquine, danazol, cyclosporine A, methotrexate) and was switched from methotrexate to leflunomide approximately 5 months before the onset of PML symptoms [76]. A second case of a 68-year-old man with a history of RA regimen being changed from azathioprine to leflunomide for 3 months, followed by manifestation and diagnosis of PML, has also been observed [77].

Long-term data on teriflunomide from the original phase II study for MS [120] with over 8 years of follow-up have shown neither a case of PML nor other opportunistic infection. The majority of infections were of the upper respiratory tract and rhinopharyngitis, with influenza and urinary tract infections also frequently reported. Serious adverse events included individual cases of appendicitis, bronchitis, pneumonia and urinary tract infection, although none of the infection-related complications led to discontinuation of the drug [121].

4.3 Dimethyl Fumarate

Fumaric acid esters have been shown to induce apoptosis of, and reduce the numbers of, certain types of T cells, particularly CD4+ cells [122]. Dimethyl fumarate (Tecfidera®) is a fumaric acid ester and an oral MS therapeutic agent approved in March 2013 by both the FDA and EMA. Fumaric acid esters have been licensed for and used to treat

psoriasis in Germany since 1994, and experimental data show anti-inflammatory as well as cytoprotective effects driven by activation of transcription factors that results in reduced expression of the NF-κB-dependent genes that regulate the expression of a cascade of inflammatory cytokines, chemokines and adhesion molecules [123, 124]. In a placebo-controlled phase III study, a significant reduction in the number of patients with relapse occurrences, annual relapse rates, illness progression and MRI lesions were described [125]. Across the three study arms, there were comparable incidences of infections reported (placebo, 65 %; dimethyl fumarate twice daily, 64 %; and dimethyl fumarate three times daily, 68 %), with serious infections occurring in approximately 2 % of all groups. There were no opportunistic infections reported, even in patients in whom lymphocyte counts below 0.5×10^9/l were encountered. During the study that compared two dimethyl fumarate dosages with placebo and glatiramer acetate, treatment infections in both study arms of dimethyl fumarate were reported in 56 % of cases versus 50 % of patients treated with glatiramer acetate or placebo [126]. Reported infections included rhinopharyngitis, bronchitis, infections of the upper respiratory tract, urinary tract infections, sinusitis and gastroenteritis. Opportunistic infections were not seen and the frequency of serious infections was low across all groups (1–2 %). There have been reports of significantly reduced lymphocyte counts, and as many as five papers have been published regarding PML associated with the use of fumaric acid esters in other diseases [78, 79, 127–129]. In some cases, there may have been other risk factors (including a history of sarcoidosis and/or the use of efalizumab), while long-term use and the low lymphocyte counts that may sometimes be encountered with the use of this drug appear to increase risk. A documented case of PML in a patient treated primarily with dimethyl fumarate for MS was recently reported [80]. Described is a 55-year-old woman who had been diagnosed with MS years earlier and who was initially treated with glatiramer acetate was enrolled in a clinical trial and treated for 4 years with dimethyl fumarate, eventually expiring secondary to PML infection and worsening in the setting of repeated acute treatments with high-dose corticosteroids. She was reported to have exhibited relative lymphopenia during the course of her treatment but the significance of this is unclear, noting lymphopenia is not uncommon with the use of this agent.

5 Therapies Under Investigation for MS

In addition to those aforementioned, there are a handful of other drugs that have been studied or may be in the pipeline for MS.

5.1 Cladribine

Cladribine and fludarabine are purine nucleosides which are cytotoxic to some resting and dividing cells, that have been used as chemotherapeutics [130]. Cladribine was studied in MS trials but has not been approved for use, and may not be [131, 132]. Incidence of PML has been associated with the similar drug fludarabine, noting this agent is used for the treatment of chronic lymphocytic leukemia, which is the most common hematological malignancy associated with PML, raising questions about the association. In most of these cases, PML developed after fludarabine therapy, and it is believed that immunosuppression resulted in JC virus activation and/or impaired clearance [72–75].

5.2 Laquinimod

Laquinimod may be an additional and relatively novel oral therapeutic option for the treatment of MS in the future [133]. This small molecule, a quinolone-3-carboxamide derivative, is an immunomodulator with anti-inflammatory and neuroprotective properties that can cross the BBB, and which has shown immunomodulatory effects in experimental studies [134]. Potential mechanisms of action include a shift of cytokine balance in favor of an anti-inflammatory Th2 profile [135] and/or modulation of the NF-κB signalling pathway [136]. In three studies, an increased number of infections of the respiratory tract were found (7.5 % with laquinimod vs. 4.5 % in placebo in the ALLEGRO study), as well as individual cases of herpes simplex and herpes zoster skin infections [137–140].

5.3 Other Monoclonal Antibodies

It is noteworthy that other monoclonal antibodies are currently being studied for use in MS. It is clear that monoclonal antibodies used as DMTs appear to interfere with the immune response in a way that may be beneficial to the disease course but which may also predispose to infection risks; natalizumab, alemtuzumab, and off-label rituximab are currently used in MS [141], while ofatumumab and ocrelizumab (agents very similar to rituximab) and daclizumab are all under clinical investigation.

We currently have significant clinical trial data in MS from daclizumab, which binds specifically to the IL-2R-alpha receptor (CD25) and is used to prevent kidney transplant rejection, but also showed reduction in MRI lesions and disability in MS trials [142–145]. In a randomized phase II study that investigated daclizumab as add-on therapy to IFN-β (CHOICE), the most frequent serious adverse events were infections (7 % with daclizumab/IFN vs. 3 % with placebo/IFN) [145, 146]. Serious adverse events were reported in 13 % of patients treated with

daclizumab compared with 5 % in the control group, of which infections were the most frequent (5 % in the daclizumab/IFN group vs. 1 % under placebo/IFN), noting no reported opportunistic infections or fatalities associated with infections. In the SELECT study, a placebo-controlled trial comparing daclizumab doses of 150 or 300 mg every 4 weeks subcutaneously which showed benefit over the placebo group, severe infection-related complications appeared in 2 % of patients receiving daclizumab and none receiving placebo. Of note, in six of these seven patients with 'severe infection' therapy was continued after the infection subsided. Of note, oral herpes infections occurred in 5–6 % of patients in all three groups, and in each group one case of herpes zoster was observed [147].

6 Best Practice and Risk Mitigation

Immune mechanisms are pivotal in the disease process of MS, and treatments have made a significant impact on the disease course. DMTs selectively interfere with the immune system in ways that modulate function, and benefits must be weighed against risks with their use. Experience teaches us that we may be able to better prognosticate the amount of risk, and decrease, or even prevent, complications through diagnostic testing or surveillance prior to and during treatment. The majority of infections that have been reported from clinical trials of the drugs currently used for the treatment of MS have been mild but some of the safety signals are more serious.

While the established safety of the platform therapies is reassuring and the incidence of opportunistic infections remains extremely low across all therapies, the effect of newer disease-modifying drugs on susceptibility to not only outside infections but also the suppression of latent infection remains questionable; the recommendation to rule out latent TB in individuals being considered for teriflunomide and alemtuzumab is a well-taken point to this effect. Checking varicella zoster virus antibody status and immunization with varicella zoster virus vaccine for those who are seronegative has been recommended for patients prior to starting treatment with fingolimod [148] and alemtuzumab [149]. A similar approach may be warranted for other DMTs where complications of varicella zoster virus have been encountered, such as with natalizumab, although it is not explicitly written in the prescribing information for other drugs. Infections or reactivation of viruses in the herpes family appear to occur with greater frequency than otherwise anticipated with some of the newer DMTs as a whole. There is some indication that antiviral prophylaxis may be protective in the case of alemtuzumab and it is recommended in the prescribing information [150] although a decision on how to initiate this is left up to providers. A similar approach with additional drugs may ultimately prove to be warranted but this recommendation may require further study.

JC virus antibody testing, with results reported as indeterminate, positive or negative, now includes index values, providing additional opportunity for risk stratification and mitigation. Overall, natalizumab should be used cautiously in patients who are JC virus seropositive, given the associated increase in the risk of developing PML. Individuals who have received prior immunosuppressive therapy are at higher risk of developing PML, and natalizumab should also be administered cautiously in this setting. Most cases of PML have not occurred until after 24 or more infusions of natalizumab. Therefore, there may be a window of opportunity to use the drug relatively safely in individuals previously naïve to said treatments, perhaps even in light of positive antibody status. It is also possible that despite increasing risk with time or positive serologic testing, use may be warranted by clinical circumstances. The Tysabri® Outreach Unified Commitment to Health (TOUCH) program is, in large part, designed to identify natalizumab-treated patients who display early symptoms of PML. A similar risk evaluation management strategy (REMS) program is also in place for the use of alemtuzumab. Experience with natalizumab-associated PML has demonstrated that early recognition is key to recovery in PML, and a high index of suspicion needs to be maintained for individuals at risk in order for the disease to be recognized as soon as possible [81].

It may be beneficial to know an individual's JC virus antibody status or index over time as a patient's status can change and viral replication during the weeks or months leading up to PML may provide sufficient stimulus for increased antibody production and detection. The observation of moderate to high, or rising, JC virus antibody titers in 22 of 25 patients with PML in whom this data have been published is supportive of the idea of using titer levels to further stratify risk with the use of natalizumab [149]. A more recent paper reported that a cohort of natalizumab-treated PML patients with samples available at least 3–6 months prior to clinical diagnosis of PML consistently demonstrated higher anti-JC virus antibody levels, rather than increases prior to clinical onset of disease. This second set of authors argued that increases in levels of anti-JC virus antibodies reported in the Plavina [149] paper were at the time of clinical diagnosis of PML and against using rising titers as a screening tool [150]. We would maintain that more frequent testing could allow for detection of rising levels, and potentially be helpful in earlier detection of PML infection. Generally, we have much to learn about using JC virus antibody testing and indices.

While there may be reasons for knowing more than whether the result is a simple negative or positive, negative

antibody status certainly does seem to indicate less or increased risk of complication of PML with natalizumab therapy. Although unproven, JC virus antibody testing data may be applicable to assessing PML risk associated with therapies other than natalizumab, with acknowledgement that the risk is much lower with other MS therapies based on what we currently know about the incidence of PML with these therapeutics (Fig. 1). In all, clinical suspicion or prior exposures may prompt surveillance of antibody status in MS patients aside from those currently being considered for, or treated with, natalizumab.

MRI or lumbar punctures can also be helpful tools for investigating potential infectious complications of therapies. MRI scans may not only help track disease but can also pick up potential complications of PML, even before clinical symptoms are present; this has led many to suggest serial scanning after 2 years of natalizumab, or in other specific scenarios where there is interpreted risk. We would argue that it is almost always helpful to have an MRI at the discontinuation and/or start of a DMT, and this can be particularly helpful in regard to the use of a therapy such as natalizumab. When suspicion of PML, varicella zoster virus, herpetic infection or other CNS infection is high enough, a lumbar puncture may be essential to the diagnosis; however, we do not think there is reason to recommend serial or surveillance spinal fluid analyses at this time.

Although less proven, other considerations such as monitoring T and B lymphocyte counts in MS patients on drug may guide the selection of therapeutic agent and dosing. Lymphopenia may contribute to risk of infections, including that of PML or other, and there are arguments that we should consider cutoff values to hold or even discontinue therapies associated with significant risks. The data are not robust and given the small number of complications encountered with a drug such as dimethyl fumarate, and the apparent lack of association of lymphopenia and infections with fingolimod, it is not entirely clear if we should use absolute cutoff values at this time. We would say that lymphopenia developed in the setting of DMT dosing should prompt careful consideration of continued use. Just as discussions of understood risk and patient's interpretation and willingness to accept the same may be appropriately unique from one person to the next, each case and course of treatment deserves an individualized approach and considerations in light of previous therapies and disease course.

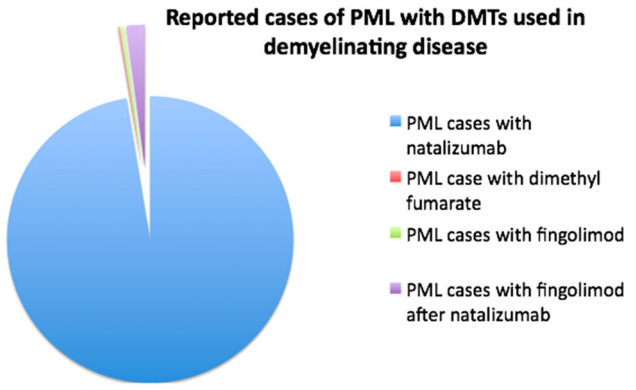

Fig. 1 Reported cases of PML with DMTs used in demyelinating disease. *MS* multiple sclerosis, *PML* progressive multifocal leukoencephalopathy, *DMTs* disease-modifying therapies

7 Conclusions

We may encounter new concerns in the near future, such as infectious diseases not previously considered or increased incidence of rare complications over time. As we expand the armamentarium of available therapies for MS, vigilance for infectious complications is essential. There are a number of screening measures recommended to assess for risk associated with therapies, including ruling out evidence of TB prior to the use of teriflunomide, assessing for antibodies to varicella zoster virus with a recommendation to immunize and allow for development of protection in patients who test negative prior to the use of fingolimod or alemtuzumab, and following JC virus antibody status to better understand, interpret and discuss the risk of PML with patients receiving natalizumab therapy (Fig. 2).

We have stressed that one should exercise caution with the use of high-dose corticosteroids in the setting of administration of some of our newer therapies, and maintain vigilance in ruling out infection before dosing. We have introduced other potential risk mitigation strategies as best understood today (not to exclude surveillance for lymphopenia and judicious use of MRI), and with growing experience we are certain to learn not only what screening measures and recommendations are most useful but also those that are most cost efficient and warranted.

Currently Approved Disease Modifying Therapies (DMTs)	Recommended Infectious Screening Measures
Interferons	
Glatiramer Acetate	
Mitoxantrone	
Natalizumab	JC Virus (JCV) Antibody Testing
Fingolimod	Varicella Zoster Virus (VZV) Immune Status
Teriflunomide	Tuberculosis (TB) Screening
Dimethyl Fumarate	
Alemtuzumab	VZV immune status and TB screening

Fig. 2 Recommended screening measures for the approved multiple sclerosis therapies

The propagation of new DMTs provides additional options for the MS community and physicians while also raising questions regarding infectious concerns—increased comfort levels with their use and tweaking of best-practice recommendations will require more experience. Low frequencies of the occurrence of many of the mentioned infections and lack of large amounts of data regarding testing and risk mitigation precludes further meaningful recommendations at this time. In all, a number of infectious diseases have been well-recognized and described as complications of the therapies currently employed in MS, and we should continually strive to minimize these risks as discussed and as best as we currently know how.

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