REVIEW ARTICLE

Progressive Multifocal Leukoencephalopathy Risk Mitigation: A Focus on Approved Immunomodulatory Drugs for Multiple Sclerosis Treatment

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Abstract

Although treatment options increasingly offer improved efficacy for multiple sclerosis, some have also resulted in an increase in treatment-related risk. Progressive multifocal leukoencephalopathy is an unusual, complex infection typically attacking the central nervous system of an individual with a weakened immune system. Attributed to the infestation of the John Cunningham Virus, it has also been found in association with several multiple sclerosis therapies. Progressive multifocal leukoencephalopathy cases have been directly associated with the use of natalizumab, dimethyl fumarate, fingolimod, and ocrelizumab for the treatment of multiple sclerosis. Alemtuzumab and mitoxantrone have been linked to progressive multifocal leukoencephalopathy in treating diseases other than multiple sclerosis, and no progressive multifocal leukoencephalopathy cases have been reported in multiple sclerosis patients. This review will examine progressive multifocal leukoencephalopathy cases associated with multiple sclerosis therapies, strategies to decrease susceptibility to progressive multifocal leukoencephalopathy, and strategies to discontinue higher-risk treatments in favor of lower-risk therapy.

Keywords

Progressive multifocal leukoencephalopathy; Natalizumab, Dimethyl fumarate; Fingolimod

Introduction

Existing approaches implemented to address multiple sclerosis (MS) are drastically evolving. There are now more than 14 approved disease-modifying therapies, which have different potency and side effect profiles. Knowledge of the side effects is required to identify the most favorable outcomes. One uncommon but serious side effect is progressive multifocal leukoencephalopathy (PML).

First coined in the 1950s, PML is an uncommon infection of the central nervous system (CNS) attacking the body when it is unusually vulnerable. The presence or reactivation of John Cunningham

Virus (JCV) is known to make individuals susceptible to PML[1]. Progressive multifocal leukoencephalopathy can cause extreme incapacitation or, in worse cases, death. Its incidence is greater in immunosuppressed individuals and those with autoimmune diseases, such as MS, systemic lupus erythematosus and rheumatoid arthritis (RA), who are treated with disease-modifying immunosuppressive therapies. Progressive multifocal leukoencephalopathy occurs as a result of JCV entry into the brain and infection of oligodendrocytes. Subsequently, brain injury starts to evolve. The clinical presentation is diverse. Neurobehavioral, motor, language and visual impairments are the most widely known manifestations of PML. Before the onset of the clinical symptoms, there was a prodrome between three and six months. At this asymptomatic stage, a detectable lesion can be seen in brain magnetic resonance imaging (MRI). Usually, it starts as a small subcortical lesion, with no contrast enhancement, and as the disease progresses, the lesions grow, and the patient starts to have symptoms[2]. Progressive multifocal leukoencephalopathy diagnosis requires a high index of suspicion, and surveillance MRIs are essential to monitor any PML-like lesion. In the case of query MRI lesions or clinical symptoms, obtaining cerebrospinal fluid (CSF) study for JCV is the first diagnostic step[3,4].

No antiviral medications for PML have been shown to be efficacious; however, suspension of the disease-modifying treatment (DMT) and, if possible, plasmapheresis, such as in the case of natalizumab, are essential steps in the treatment of PML. Restoration of immune system will help control infection. However, this occasionally leads to a paradoxical immune reaction. Immune reconstitution inflammatory syndrome (IRIS) can cause brain edema and worsen clinical disability. Therefore, PML is a serious disease with high mortality and morbidity rates[5]. To date, PML cases among individuals with MS treated with natalizumab, dimethyl fumarate (DMF), *fingolimod and ocrelizumab* have been recorded[6,7]. This review will focus on these four DMTs and their association with PML.

Natalizumab

Natalizumab is a humanized monoclonal antibody for the treatment of relapsing forms of MS and Crohn's disease (CD). It is considered one of the most potent and effective therapies for MS that worsens following remission[8-10]. Natalizumab attaches to the α4 subunit of the α4β1 receptor on lymphocytes. It interferes with lymphocyte α4-facilitated attachment to the vascular endothelial lining, which prevents the diffusion of activated lymphocytes through the blood-brain barrier and subsequently reaches the brain[11].

Three instances of PML were recorded in 2005 among patients enrolled in clinical trials for natalizumab. There were two deaths: a patient with MS who was also receiving intramuscular interferon-1a[12,13] and the other a patient with CD who was taking other immunosuppressants[14]. Several incidents of PML affliction were also observed in patients not enrolled in clinical trials who were not taking other disease-modifying medications concurrently. By March 2019, a total of 814 cases of PML had been reported in natalizumab-treated individuals (811 in MS and three in CD). Worldwide, PML incidence rates among natalizumab-treated subjects are 4.14 for every 1,000 patients (95% CI 3.86 to 4.43 per 1,000 patients), with doses as low as eight and as high as 148. Natalizumab intake among the same subjects was 51 months on average[15]. (Biogen data).

There are three factors associated with potential susceptibility to PML in individuals receiving natalizumab: the presence of JCV immunoglobulins (indicating prior infection with the JCV), prolonged drug course (>24 months), and being previously subjected to an immunosuppressant[16,17]. The merits and tradeoffs of sustaining natalizumab therapy need to be considered carefully for patients with these risk factors.

1. JC Virus Status

Among patients receiving natalizumab, those without JCV immunoglobulins have the lowest susceptibility to PML, with an incidence rate of only 0.1 in 1,000[15]. Susceptibility among patients testing positive for the antibody accounts for an incident rate of 3.8 in 1000[17].

The use of an anti-JCV antibody index was purported to help mitigate the potential of developing PML, but its efficacy has been questioned, as the case numbers have continued to rise steadily despite the introduction of the antibody test more than 5 years ago[18]. When antibody testing became available for MS patients taking natalizumab, it was suggested that patients with higher anti-JCV antibody titers were at increased susceptibility to PML compared to those with

lower titers[18]. From existing data, an anti-JCV antibody index value of ≤ 0.9 is associated with low susceptibility to PML, and the risk is significantly amplified at values above 1.5. The risk significantly increases if the patient has prior immunosuppression and more than two years of treatment[19]**.** Repeat testing every six months is suggested for MS patients receiving natalizumab doses to evaluate risk of seroconversion and false negative test results. The rate of patients initially testing negative but eventually becoming positive is 8% annually in natalizumab-treated patients compared to the general rate, which is 1%[20]. Approximately 2.2% of cases of false negative test results were reported[15]**.**

2. Duration of Treatment

Prior studies indicate that 1-12 doses of natalizumab are less likely to predispose patients to PML (0.05 per 1000 patients); however, the incidence increases with increasing infusions, as 13-24 infusions and 25-36 infusions lead to PML infections in 0.73 and 1.49 in 1,000 patients, respectively. From existing data, the majority of patients developing PML receive 49-60 doses (2.20 per 1,000 patients), and this rate levels off at 61-72 infusions (1.67 per 1,000 patients). Information on patients who have had more than 72 doses remains scant. After two years of treatment, health providers recommend biannual check-ups for patients who have not taken immunosuppressants and have low JCV index values[19,21].

3. Prior Immunosuppressant Use

Cytotoxic agents have been found to predispose natalizumab-treated patients to PML. These include mitoxantrone, azathioprine, methotrexate, cyclophosphamide and mycophenolate mofetil[12]**.**

In general, patients with amplified susceptibility to PML (positive JCV antibody, prior immunosuppression and a course of natalizumab exceeding two years) should be monitored more frequently. Similarly, quarterly to semiannual clinical assessment and MRI using an abbreviated MRI protocol (FLAIR, T2-weighted and diffusion weighted imaging) are recommended[10].

Proangiogenic factor matrix metalloproteinase 9 (MMP 9) is a recently identified biomarker that may play a role in PML risk stratification. It was found that patients developing natalizumab-related PML had a significantly lower MMP 9 level at baseline and continued to show low levels until PML developed compared with patients taking natalizumab who did not develop PML. This biomarker will, however, require greater validation before it is widely implemented[22].

Even among patients initially testing negative for PML, contraction of the infection was also observed sometime after cessation of natalizumab dosing. Therefore, approximately 6 months after discontinuation of natalizumab therapy, physicians should continue to monitor patients for any new signs and symptoms that may suggest PML[19,23].

In PML cases related to natalizumab therapy, immediate discontinuation of the drug and plasmapheresis has been the standard treatment. However, immune reconstitution IRIS was subsequently found to afflict patients following drug cessation. This phenomenon was first seen in acquired immune deficiency syndrome (AIDS) patients after instituting highly active antiretroviral therapy. Immune reconstitution inflammatory syndrome is an inflammatory response that paradoxically occurs as a reaction of the salvaged immune system to the virus. Due to the decrease in saturation of natalizumab in the blood, lymphocyte trafficking to the central nervous system (cellular immunity) is restored. Restoration of immune system function leads to a fast deterioration of previous neurological losses, as confirmed by MRI results manifesting as enlarged lesions and increased contrast enhancement. Reconstitution of the immune system is essential to reverse PML. Immune reconstitution inflammatory syndrome is seen early in patients who receive plasma exchange as a result of accelerated clearance of natalizumab[24,25].

Even without PML, several MS patients still exhibited worsening disease activity after natalizumab treatment, implying the potential occurrence of IRIS even in the absence of a viral infection. This is known as natalizumab withdrawal syndrome. In some cases, the disease that emerges is even worse than the baseline disease before starting natalizumab, leading to the discussion as to whether this represents a "rebound" of disease[26–28]. This development points out that some drugs, such as natalizumab or fingolimod, do not eliminate disease-causing cells but only

impair their trafficking and lead to the potential development of ricocheting disease activity. This is a critical consideration when determining a wash-out period before changing to other DMTs or suspending treatment for reasons such as pregnancy.

Fingolimod

The mechanism of action is by targeting sphingosine-1-phosphate receptors, which prevents activated lymphocyte release. This leads to reduced autoregressive lymphocyte infiltration into the CNS[29–31].

Contraction of PML by patients undergoing fingolimod therapy has also been recorded. Approximately 28 PML cases in >284,000 fingolimod-treated patients had been reported by the end of May 2019. However, some of these cases cannot be attributed solely to fingolimod, as patients had been switched from natalizumab, or there were confounding factors (such as a prior history of cancer or ulcerative colitis/immunosuppressive therapy). Exposure to fingolimod, for the majority of patients, was more than two years, with exposure ranging from 18 to 84 months[32]. None of the patients had a sustained lymphocyte count of ≤200 cells/μL, known as severe lymphopenia[33] (Novartis data).

Progressive multifocal leukoencephalopathy incidence among patients solely undergoing fingolimod therapy is very low, estimated at less than 0.099 in 1,000 patients (95% confidence interval[CI]: 0.065, 0.142); this corresponds to ~1:10,100 patients (Novartis data). No clear pattern or risk factor has been associated with PML cases in patients administered fingolimod, but older age (average age in this study was 53) and longer treatment duration seem to be associated with most PML cases. A low lymphocyte count has not been associated with PML cases in fingolimod.

According to the Berger criteria for PML diagnosis[34], 14 cases of definite or probable PML with a history of natalizumab therapy were reported. The risk of PML in fingolimod-treated patients who switched from natalizumab is 0.46 per 1,000 patients who are assumed to have taken natalizumab (15% of fingolimod patients)[32].

Approximately 0.099 per 1,000 patients undergoing fingolimod treatment appear to have a lower risk than that seen in JCV antibody-negative natalizumab patients (<1/1,000).

Due to the low number of cases, changing the monitoring standards for prolonged fingolimod treatment is not recommended. However, remaining vigilant towards signs suggestive of PML is required of all patients. Regular clinical assessment and MRI surveillance (at least once yearly) for early detection of PML are important to improve clinical outcomes. In cases of suspected PML, fingolimod should be discontinued until the possibility of PML is ruled out.

The progression of the disease can be exacerbated in an aggressive flare up almost immediately upon fingolimod cessation, indicating a ricocheting effect similar to that after natalizumab discontinuation[16]. Most of these cases occur 4-8 weeks after discontinuation, associated with the increase in peripheral lymphocyte count[33,35,36]. Susceptibility to this rebound effect is not yet well understood, but generally, rapid disease progression prior to the commencement of treatment is among the risk factors following treatment cessation. Rebound can potentially occur as early as four weeks after halting fingolimod therapy and may persist even with the use of steroids or immune therapy (*i.e.,* rituximab)[26,37]. If fingolimod withdrawal is necessary, patients must be made aware of this possibility and monitored closely[33].

Dimethyl fumarate (DMF)

How DMF functions is not well understood. It increases cytosolic levels of nuclear factor erythroid 2-related factor 2, which has immune regulatory and antioxidative effects on oligodendrocytes, neurons, and glial cells[14]. Dimethyl fumarate is a transformation product of fumaric acid (FA), a platform chemical that has been used for decades to treat psoriasis[38,39]. Only 6 PML incidents were observed among those who were administered FA. It is also worth noting that these patients had used immunosuppressants or had other PML risk factors[40–44].

As of June 2019, seven confirmed PML cases with DMF had been reported out of more than 398,000 patients worldwide (less than 1 confirmed DMF-associated PML case per 100,000 patient-years).

To the best of our knowledge, only four PML incidents have been recorded in DMF-treated patients without prior exposure to PML-causing agents such

as natalizumab. Proposed risk factors for PML in DMF-treated patients include low lymphocyte counts and longer treatment duration[45]. Six of the seven PML cases related to DMF had persistent grade 3 lymphopenia (below 0.5x10^9/L) (Biogen data). However, lymphopenia is not an uncommon adverse effect with DMF and could be one of the biomarkers for the drug to control the disease[46]. Measures to mitigate PML risk in patients receiving DMF should include increased vigilance in lymphocyte monitoring. In cases of persistent > 6 months grade 3 lymphopenia (below 0.5x10^9/L) while on DMF, the benefits and risks of this treatment should be reconsidered[45]. Although there are no defined risk factors for PML in DMF-treated patients, PML has never been observed without JCV. We propose that if an anti-JCV antibody test is positive for a patient with a persistent low lymphocyte count, vigilant surveillance is necessary, and options for changing the course of treatment should be discussed with the patient.

Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody targeting CD-20 on B-cells to tackle relapsing remitting MS and primary progressive MS. As of May 2019, more than 100,000 patients started taking ocrelizumab worldwide. While PML cases had been observed in patients who received the drug, all the cases were assumed to be related to other DMTs. One PML case was related to previous exposure to fingolimod. The other six patients had been treated previously with natalizumab (Roche data). It seems that ocrelizumab is a low risk DMT for PML.

Transitioning between drugs

Despite the absence of specific guidelines, a few evidence-based practices have been reported (Fig. 1). Fingolimod and DMF result in lower levels of circulating

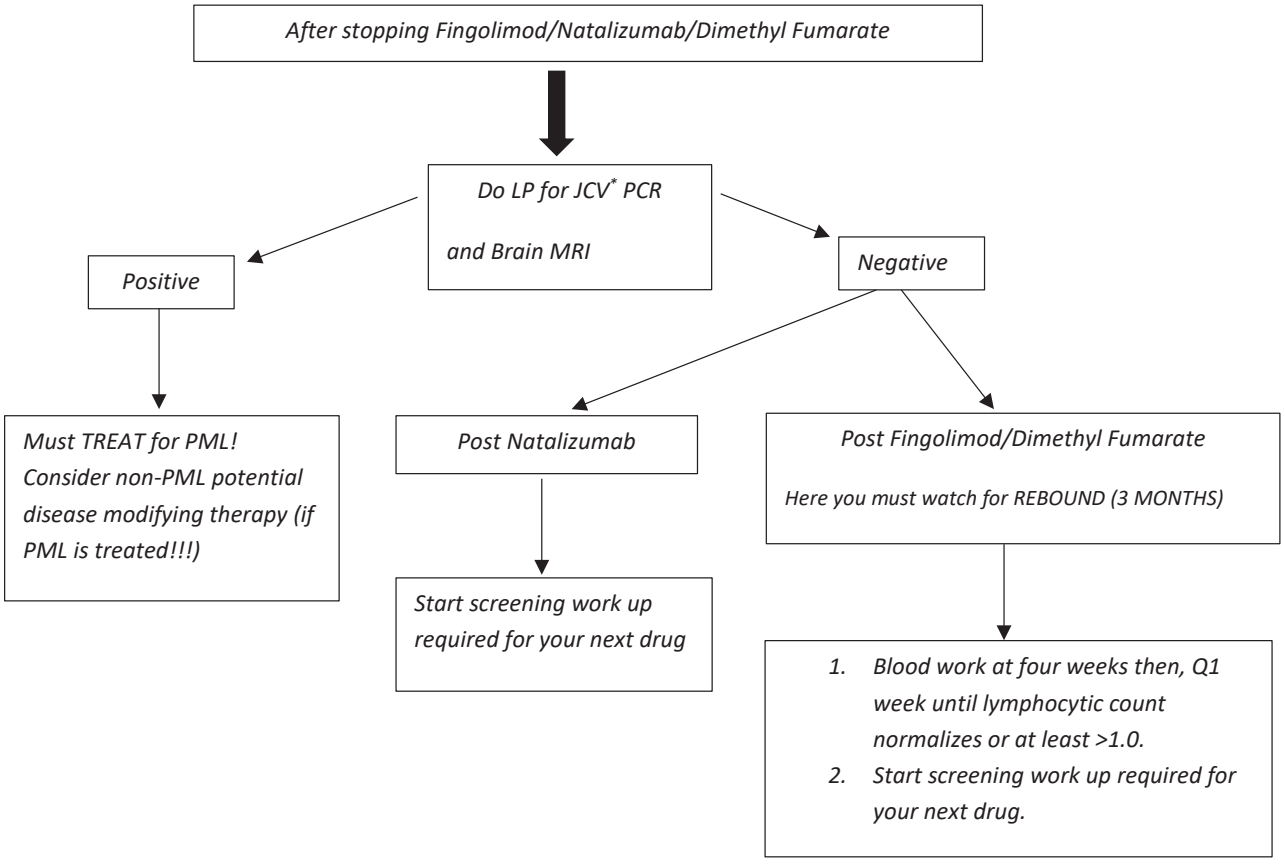

Figure 1. Transitioning between progressive multifocal leukoencephalopathy potential drugs algorithm. (LP: ; JCV*: John Cunningham virus; PCR: Polymerase chain reaction; MRI: Magnetic resonance imaging; PML: Progressive multifocal leukoencephalopathy)

lymphocytes, but they do so via different mechanisms. When switching the treatment from a therapy that lowers lymphocyte counts (*i.e.,* fingolimod and DMF) to a therapy that targets circulating lymphocytes, such as alemtuzumab, waiting until lymphocyte counts begin to recover is advisable, which typically occurs between 4 and 8 weeks following halting of treatment[25]. It is thought that re-entry of lymphocytes into the CNS will precipitate a relapse of disease activity. Therefore, a suggested wash-out period is approximately four weeks[29,31,47]. At present, the shortest recorded rebound period is four weeks. Unfortunately, even with this short wash-out period, the risk of MS relapse is not eliminated[48].

The mechanism of natalizumab is insignificant in regard to circulating lymphocyte counts. Instead, it prevents their diffusion into the CNS[49]. Therefore, a wide wash-out gap with natalizumab may be more harmful than beneficial, as it may cause disease rebound[25]. The only concern is the risk of PML carry-over in JCV-positive patients. The exclusion of PML can be ascertained by an MRI brain scan and cerebrospinal fluid examination for JCV DNA prior to administering agents that might compromise the immune system, such as alemtuzumab or cladribine[5,7,50]. Both natalizumab and fingolimod produce long-lasting immunosuppression following even a single course of therapy, and their immediate impact is irreversible. If persistent PML develops after the use of these immunosuppressive drugs, it is likely that the patient will not be able to completely eliminate the virus as a result of poor repopulation of immune cells. The implementation of an alternative therapy such as teriflunomide can be used to prevent relapses that may occur as part of the drug withdrawal syndrome, eliminating risk of PML before immunosuppressive treatment.

Mitigating Progressive Multifocal Leukoencephalopathy Risk

Progressive multifocal leukoencephalopathy is a rare but serious risk of several approved DMTs. The incidence and risk stratification are much clearer in the case of natalizumab compared to other therapies, namely, fingolimod and DMF, as there are a greater number of cases seen with natalizumab.

Natalizumab effectively minimizes MS relapses and slows deterioration, but the benefits may be offset by the risk of PML, as well as the risk of rebound disease. Cases of PML traced back to the use of natalizumab must urgently be addressed to alleviate its negative neurologic effects and prevent mortality. Moreover, the advantages and tradeoffs in use of the drug must be carefully evaluated. Considering the patient's duration of therapy, prior immunosuppression, and the JCV virus index can help mitigate the risk.

The treatment of PML is still empirical. Plasmapheresis was identified as a potential way to rapidly eliminate the body of natalizumab and restore a normal immune system to fight PML. However, it is not known whether plasma exchange can change the outcome of PML following either fingolimod or DMF treatment. A recent study showed no significant difference in the survival rate or clinical outcome between plasma exchange-treated PML and those who did not receive plasma exchange. Plasma exchange was also found to accelerate IRIS[51]. Progressive multifocal leukoencephalopathy - Immune reconstitution inflammatory syndrome has an impact on survival and neurologic outcome. Corticosteroids are an option for natalizumab-associated PML-IRIS. Recent reports suggest a possible role for maraviroc, a CCR5 suppressant known to combat HIV by inhibiting CCR5-expressing cells from trafficking to the CNS[52].

Progressive multifocal leukoencephalopathy following DMF or fingolimod is still very rare and does not compare with the risks of natalizumab. Careful patient selection and monitoring minimizes the risk of PML. As a reference point, a baseline MRI taken within the previous 3 months is utilized. Should suspicion of PML infection arise, treatment must be suspended until PML has been excluded. MRI, preferably with contrast, should be performed immediately along with CSF testing for JC viral DNA (polymerase chain reaction). Low lymphocyte counts are not thought to be a risk factor in fingolimod-associated PML. For DMF, a complete blood count prior to treatment and quarterly throughout the entire course of therapy is recommended. Should lymphocyte count drop significantly for a prolonged period of six months, discontinuing treatment should be considered. If treatment continues, patients should be closely monitored, both clinically and radiologically.

The switch between DMTs is complicated, and specific gaps in treatment duration may be necessary. Evidence-based recommendations for switching from one MS treatment to another and for wash-out periods

are needed to minimize PML susceptibility while at the same time controlling MS symptoms, especially with medications that tend to have a rebound effect, such as fingolimod and natalizumab.

This review is not intended to be an all-encompassing evaluation of the total cases of DMT-associated PML. Nevertheless, it attempts to provide some guidelines for stratifying and mitigating the risks of treatment-associated PML in MS with the expanding array of new immunomodulatory drugs.

Conclusion

With the expanding treatment options for MS and the introduction of highly potent immunological drugs, challenges are not limited to choosing the best drug for each patient but to the safety issues of each drug. PML is one the most feared complications and has a well-known association with MS treatments, such as natalizumab. Progressive multifocal leukoencephalopathy has been reported with other drug treatments, such as DMF and fingolimod, whose risk factors are not well understood. Understanding the immunological mechanism of each treatment and the possible interaction between them could minimize the risk of PML. Switching between therapeutic drugs to minimize the risk of PML is another challenge that can lead to the rebound of disease activity or IRIS. We know from observing these drugs in clinical practice that short wash-out periods between therapies are reasonable, and vigilant surveillance of PML in high-risk patients is warranted. As more therapies are expected to be approved soon, susceptibility to opportunistic infections, such as PML, will be a serious concern; however, randomized controlled trials of opportunistic infection in high-risk populations are not feasible. We will continue to gain information from longer-term prospective studies to help identify risk factors and how to properly switch between different therapies.

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Conflict of Interest

The authors declared that there is no conflict of interest that is related to this study and this article.

Disclosure

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Ethical Approval

The study was approved by the Ethics Committee of the KAUH in Jeddah, Kingdom of Saudi Arabia, also known as the Institutional Review Board of Hospitals.

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التخفيف من مخاطر اعتلال بيضاء الدماغ متعدد البؤر التقدمي: التركيز على الأدوية المعدلة للمناعة المعتمدة لعلاج التصلب المتعدد

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المستخلص. على الرغم من أن خيارات العلاج تقدم بشكل متزايد فعالية محسنة لمرض التصلب المتعدد ، فقد أدى بعضها أيضًا إلى زيادة المخاطر المرتبطة بالعلاج. اعتلال بيضاء الدماغ متعدد البؤر التقدمي هو عدوى غير عادية ومعقدة تهاجم عادة الجهاز العصبي المركزي لفرد يعاني من ضعف في جهاز المناعة. يعزى إلى الإصابة بفيروس جون كاننهام، كما تم العثور عليه بالاشتراك مع العديد من علاجات التصلب المتعدد. ارتبطت حالات اعتلال بيضاء الدماغ متعدد البؤر التقدمي بشكل مباشر باستخدام ناتاليزوماب وثاني ميثيل فومارات وفينجوليمود وأوكريليزوماب لعلاج التصلب المتعدد. م ربط اليمتوزوماب وميتوكساترون باعتلال بيضاء الدماغ متعدد البؤر التقدمي في علاج أمراض أخرى غير التصلب المتعدد، ولم يتم الإبلاغ عن حالات اعتلال بيضاء الدماغ متعددة البؤر التقدمية في مرضى التصلب المتعدد. ستفحص هذه المراجعة حالات اعتلال بيضاء الدماغ متعددة البؤر التقدمية المرتبطة بعلاجات التصلب المتعدد، واستراتيجيات لتقليل القابلية للإصابة باعتلال بيضاء الدماغ متعدد البؤر التدريجي، واستراتيجيات التوقف عن العلاجات عالية الخطورة لصالح العلاج منخفض المخاطر.

الكلمات المفتاحية: اعتلال بيضاء الدماغ متعدد البؤر التقدمي. ناتاليزوماب ، ثاني ميثيل فومارات ؛ فينجوليمود