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Risk Mitigation Strategies for Adverse Reactions Associated with the Disease Modifying Drugs in Multiple Sclerosis

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Abstract

Over the past several years the number of disease modifying therapies (DMTs) have doubled in number. The thirteen approved agents have shown a wide-range of efficacy and safety in their clinical trials and post-marketing experience. While the availability of the newer agents allows for a wider selection of therapy for clinicians and patients, it requires careful understanding of the benefits and risks of each agent. Several factors such as the medication efficacy, side-effect profile, patient's preference, and co-morbidities need to be considered. An individualized treatment approach is thus imperative. In this review, risk stratification and mitigation strategies of the various disease modifying agents will be discussed.

1. INTRODUCTION

Since the introduction of β-interferons in 1993, the field of multiple sclerosis (MS) departed from a purely diagnostic and symptomatic treatment approach to one that is directed at disease modification. Still, it was not until several years ago that our treatment options vastly expanded. Prior to the availability of multiple agents the treatment approach was mostly based on the patient's preference given the relatively similar efficacy and side-effect profile of the agents.

As of August 2015, thirteen disease-modifying therapies (DMTs) have been approved in the North America and Europe with many more in the pipeline. However, while these agents have shown efficacy, they are not risk free, and often the choice of DMT is based on a combination of its efficacy, side-effect profile, patient's preference, and co-morbidities. This review will focus on the risks associated with the various DMT and how they can be mitigated.

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Compliance with Ethical Standards:

2. INTERFERON BETA (IFN-β)

Beta-Interferons inhibit T-lymphocyte activation and proliferation by down-regulation of major histocompatibility complex (MHC) class II expression on antigen presenting cells (APCs) as well as impairing the interaction of CD40L and CD28 on T cells [1]. IFN-β also affects the blood brain barrier by increasing vascular cell adhesion molecules (VCAM), which block leukocyte adhesion to the endothelium via very late antigen-4 (VLA-4). Formulations of IFN-β 1a and 1b are available as either intramuscular or subcutaneous injections. In 2014, a pegylated form of IFN- β 1a was approved, decreasing the administration frequency to twice monthly.

IFN-β has a long safety track record, with the exception of the pegylated form, which was approved in 2014 but is expected to have a similar safety profile. Despite their relative safety, IFN-β products have a significant number of adverse effects that could impact patient compliance. Injection site reactions and skin necrosis can be seen with subcutaneous forms of IFN-β. These can be avoided by proper aseptic techniques, rotating injection sites and applying ice to the site prior to the injection [2]. Post-injection flu-like symptoms are universal among the interferons, especially within the first few months on treatment [3]. Patients may experience a constellation of symptoms such as headache, fever, chills, fatigue, malaise, and myalgias that tend to dissipate over time after the injection. Use of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDS) have been shown to be effective at mitigating this reaction [4].

There is debate whether IFN-β worsens depression, which is common among MS patients [5–8]. Regardless, patients should be screened for signs of depression or suicidal ideations and standard anti-depressive medications can be considered if necessary (i.e. psychotherapy, selective serotonin reuptake inhibitors, serotonin and noradrenergic reuptake inhibitors, and tricyclic antidepressants). If depression remains intractable to treatment, alternative DMTs should be considered.

Patients on IFN-β should have a complete blood count (CBC) and a comprehensive metabolic panel (CMP) checked, every 6 to 12 months, as mild transaminitis and leukopenia may occur [9]. A few cases of thrombotic thrombocytopenic purpura (TTP) have been reported in patients on IFN-β [3, 9]. Alteration in thyroid function has been seen, thus intermittent assessment is recommended [10]. Lab abnormalities can be mitigated by temporarily lowering the medication dosage, frequency or holding its administration altogether. Persistent abnormalities should prompt discontinuation of treatment and alternative therapy.

In a subset of patients on IFN-β, neutralizing antibodies (Nab) may develop [11]. These tend to occur more with high frequency formulations (subcutaneous IFN-β1b and IFN-β1a), and tend to develop within 6–18 months of treatment. Nab should be checked in patients with active disease despite being on therapy as an indication to abort and consider alternative agents.

3. GLATIRAMER ACETATE (GA)

Glatiramer acetate (GA) is a polymer of four amino acids that reduces disease activity by promoting suppressor cells, expanding regulatory T cells, and modifying APCs [12]. Since its approval in 1996, GA has shown comparable efficacy to interferons with a milder side-effect profile [13]. GA is available as 20 mg daily injections or 40 mg thrice weekly dosing. It is generally well tolerated, but some patients may experience allergic reactions or injection site reactions [14, 15]. Similar to IFN-related reactions, prior ice application, site rotation, and proper injection techniques should be applied. Consistent injection in the same sites may cause lipoatrophy. Rarely, patients may experience systemic injection reactions that are characterized by flushing, chest tightness, palpitations, dyspnea, and anxiety [15]. These reactions are self-limited and do not necessitate any specific treatment. The FDA approved a generic form of GA in April 2015.

4. MITOXANTRONE

Mitoxantrone is a chemotherapeutic agent approved for rapidly worsening relapsing MS or progressive MS [16]. As an immunosuppressant, it interferes with DNA repair, inhibits cellular migration, induces apoptosis of dendritic cells, inhibits B and T-cell function, and inhibits macrophage-mediated myelin degradation [17–19]. However, it has fallen out of favor due to dose related cardiac toxicity and hematologic side-effects [20]. To prevent the development of congestive heart failure, dosing should be limited to a cumulative 140 mg/m^2 (approximately 10 courses). As such, baseline electrocardiogram (ECG), and left ventricular ejection fraction (LVEF) evaluation via echocardiogram or multi-gated radionuclide angiography (MUGA) should be done. Once on treatment and prior to each infusion, repeat LVEF assessment is necessary [21–23]. If LVEF falls ≤50% then the medication should be discontinued. There also have been reports of delayed cardiac failure 3–5 years post discontinuation [24].

Although rare, patients on mitoxantrone may experience promyelocytic disorders such as acute myelogenous leukemia [25]. A detailed literature search by Ellis et al. concluded that the risk of leukemia increases significantly once the cumulative exposure exceeds 60 mg/m^2. Amenorrhea may be experienced by women on mitoxantrone, especially in older women and those with irregular menses at baseline [23].

5. NATALIZUMAB

Natalizumab is a monoclonal antibody directed against α4-integrin of VLA-4, preventing its binding to VCAM-1 [26]. The binding prevents lymphocyte migration across the blood brain barrier and subsequently decreases inflammation. Natalizumab was approved by the US Food and Drug Administration (FDA) in 2004 after two phase 3 trials demonstrated superior efficacy of natalizumab versus placebo (AFFIRM trial) and in combination with intramuscular IFN-β1a versus IFN-β1a monotherapy (SENTINEL trial) [27, 28].

In February 2005, three patients on natalizumab developed progressive multifocal leukoencephalopathy (PML), a potentially fatal infection resulting from re-activation of latent John Cunningham virus (JCV) infection [29–31]. As a result, natalizumab was

temporarily withdrawn from the market then reintroduced in July 2006. The risk of PML in patients on natalizumab is dependent on the duration of treatment, prior use of immunosuppressive agents, and the presence of serum JCV antibodies [32]. Patients who are JCV antibody negative, regardless of treatment duration or prior immunosuppressant use, have <1 per 1000 risk of PML [33]. This low (but not zero) risk is due to the fact that two cases of seronegative JCV natalizumab-related PML were previously reported [33, 34]. Moreover, the false negative rate for the JCV antibody assay is 2.5–2.7% [35, 36]. The risk of PML however, substantially increases with JCV seropositivity and treatment greater than two years (>3/1000 risk). The prevalence of JCV antibodies in MS patients is 50–60% [35, 37, 38]. As of June 2015, the overall incidence of PML in natalizumab treated patients is 3.96 in 1000 patients [39]. Recently, a 2-step enzyme-linked immune-sorbent assay (ELISA) with quantitative index levels for JCV antibody detection was developed [36]. The test further stratifies JCV seropositive patients to those at low versus high risk of developing PML depending on their JCV antibody index. In a patient with no prior immune suppression, an index less than 1.5 has essentially 0.1 per 1000 risk of developing PML in the first 24 months of treatment, similar to the risk of a JCV seronegative patient [40]. Treatment beyond 24 months increases the risk up to 1.3 per 1000 only. Whereas those with an index >1.5 have a 1 per 1000 risk in the first 24 months, and 5–8 per 1000 thereafter. Use of the index has expanded the safety net for patients considering natalizumab but are JCV seropositive. It is worth noting however, that despite the availability of the assay and risk stratification since 2010, the incidence of PML has not changed [41]. JCV antibody should be checked at baseline prior to therapy and repeated at 6-month intervals. MRI brain should also be obtained if clinical suspicion for PML arises. Increased frequency of MRI and JCV status can be conducted in high-risk patients (long duration of therapy, prior immunosuppressants). Should patients develop PML, confirmed by the presence of JCV polymerase chain reaction (PCR) in cerebrospinal fluid, prompt 5-course plasmapharesis (PLEX) should be instituted and natalizumab discontinued [42, 43]. Patients may experience immune reconstitution inflammatory syndrome (IRIS) after PLEX and should be treated with a course of intravenous methylprednisolone [42].

Other potential adverse effects of natalizumab noted in the phase 3 trials and post-marketing experience are mainly infusion reactions within two hours of infusion [27, 28]. Headache represents the majority of infusion reactions, but patients may also experience fatigue, dizziness, and nausea [27, 28]. Hypersensitivity reactions resulting in anaphylaxis, urticaria, allergic dermatitis, or hives may occur. Allergic reactions have been associated with the presence of anti-natalizumab antibody presence [46]. In such cases, natalizumab should be discontinued and alternative therapy be considered. The risk of opportunistic infections other than PML from the phase 3 trials were <1% [27, 28, 47]. These are mostly herpetic infections (zoster and meningitis). There have been several case reports of central nervous system (CNS) lymphoma that were likely associated with natalizumab [48–52]. Liver toxicity - even autoimmune hepatitis - in patients on natalizumab were previously seen, thus routine monitoring is necessary [53, 54]. Other rare reported adverse effects include erythroblastaemia, hypereosinophilia, and natalizumab-associated JCV cerebellar granule cell neuronopathy (GCN) [44, 45, 55, 56]. Thus, baseline testing prior to natalizumab should include a CBC, liver function tests (LFT), brain MRI, and JCV antibody testing.

MS relapses during treatment with natalizumab are a rare occurrence (6% in the AFFIRM trial) [27]. Thus in patients who develop breakthrough relapses, PML should first be ruled out via imaging and cerebrospinal fluid (CSF) analysis. Active lesions on MRI indicative of MS activity prompt assessment for anti-natalizumab antibodies. In the phase 3 trials, anti-natalizumab antibodies were present in 9–12% of patients, but only 6% were persistently elevated and resulted in an increase in infusion reactions and loss of efficacy [27, 28]. The discontinuation of natalizumab is associated with prompt return of disease activity typically within 6 months [57].

6. FINGOLIMOD

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator that reduces circulating lymphocytes via sequestration in lymph nodes [58–60]. It is the first oral agent approved for the treatment of multiple sclerosis in 2010 based on two phase 3 trials, FREEDOMS and TRANSFORMS [61–63]. As a nonselective S1P receptor modulator, fingolimod exhibits target and off-target adverse effects that require vigilant monitoring. The primary off target effect is first-dose bradycardia and atrioventricular (AV) block [62–64]. The first dose reduction in heart rate is approximately 8 beats per minute, with a nadir of 4–5 hours post first dose. The incidence of first degree AV block is 4.7%, Mobitz type 1 second degree AV block in 0.2% and symptomatic bradycardia in 0.5% [66]. These first-dose observations (FDO) lead to a strict cardiac monitoring protocol recommended by the FDA and EMA for the first 6 hours post-first dose administration [61]. The monitoring process involves baseline electrocardiogram (ECG), heart rate (HR) and blood pressure (BP) measurements. During the FDO visit, the patient is monitored for a minimum period of 6 hours post administration for adverse symptoms, while obtaining hourly HR and BP recordings. The observation period may be extended if a patient becomes symptomatic or the heart rate does not begin to increase from its nadir within the period. A final ECG is obtained at 6 hours. Due to the risk of recurrence of bradycardia, the FDO monitoring process is repeated if fingolimod was discontinued for one day within the first two weeks of treatment; more than 7 days during weeks 3 and 4 of treatment, or more than 2 weeks thereafter.

Other common adverse effects include headache, hypertension, cough, dyspnea, back pain, headache, influenza, and diarrhea.[62–64]. These are treated symptomatically and investigated medically as appropriate. Macular edema was a rare, but serious adverse event that was noted in the phase 3 trials [62–64]. Patients starting on fingolimod are required to undergo ophthalmologic examination to evaluate the presence of macular edema at baseline and three months post initiation [67, 68]. Optical coherence tomography (OCT) can detect trace edema that might not be evident on dilated fundoscopy; hence not only is it an alternative, but it is superior [69]. The risk of macular edema increases in patients with diabetes mellitus, those older than 40 years of age, and possibly those with a history of uveitis [68].

The incidence of herpes infections was higher among participants on fingolimod in the TRANSFORMS and FREEDOMS II trials [62]. In fact, two patients died of disseminated primary varicella zoster virus (VZV) and herpes simplex virus (HSV) encephalitis. Baseline labs prior to fingolimod initiation should include a VZV titer; and patients with low titers

should be immunized with 2 doses of varicella virus vaccine 0.5 mL, four weeks apart [70]. Asymptomatic three-fold elevation of liver transaminases was reported in up to 10% of patients on fingolimod in the phase 3 trials, thus baseline and routine monitoring of LFT is necessary. Fingolimod decreases lymphocyte counts by 70–80% of baseline within the first month, and upon discontinuation, levels rise to the lower limit of normal within 4–8 weeks [71, 62–64]. Lymphocytopenia however, is not associated with a greater risk of infections.

Based on the clinical trials and post-marketing experience, patients on fingolimod are at a risk for certain malignancies, most of which are dermatologic. Cases of basal cell carcinoma, squamous cell carcinoma, Bowen's disease, malignant melanoma, lymphoma, breast cancer Kaposi's sarcoma, as well as lymphomatoid papulosis have been reported [72–77]. Thus adequate counseling and perhaps periodic dermatologic evaluations should be recommended.

Fingolimod is pregnancy category C as preclinical studies have shown risk of fetal toxicity [78]. Data from nine phase II, III, and IV trials (66 pregnancies) with in-utero exposure to fingolimod revealed two birth defects: unilateral bowing of the tibia, and acrania. Three elective abortions were due to developmental defects, including a case of tetralogy of Fallot. These cases emphasize the importance of counseling patients on fingolimod for adequate contraception and allow a washout period of at least two months prior to conception.

To date, there are 11 known cases of PML in patients on fingolimod with prior exposure to natalizumab [79]. In February 2015, Novartis reported a case of PML in an MS patient treated with fingolimod for four years, without prior exposure to natalizumab [80]. A routine MRI scan showed two large non-enhancing T2 lesions in the cerebellum and temporal regions, one of which had high signal intensity on diffusion weighted imaging and apparent diffusion coefficient map. The diagnosis of PML was confirmed via positive JCV serology in blood and cerebrospinal fluid PCR. The patient had no known history of medications or comorbidities associated with PML, and absolute lymphocyte counts were 240–890 cells/μL. Despite this case report, the estimated risk of PML remains low based on the observed rate in more than 114,000 patients treated with fingolimod in clinical trials and clinical practice. Hence, while patients and physicians should be diligent about monitoring for signs of PML with use of fingolimod; there are no guidelines however, regarding JCV antibody or lymphocyte count testing.

7. TERIFLUNOMIDE

Teriflunomide is an active metabolite of leflunomide, which is approved for the treatment of rheumatoid arthritis [81]. It is a reversible inhibitor of dihydroorotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis for DNA replication, thereby decreasing B- and T-cell activation and proliferation [82, 81, 83]. Teriflunomide was approved for relapsing MS based on two phase 3 trials TEMSO and TOWER [84, 85].

Teriflunomide has black box warnings for hepatotoxicity and teratogenicity, which were carried over from its parent drug leflunomide [88]. In the TEMSO, TOWER, and TOPIC trials, there was a higher incidence of elevated alanine transaminase levels (ALT) ≥3 times upper limit of normal (ULN) in patients on teriflunomide than placebo [84–86]. However, in

the TENERE trial, the incidence was not greater compared with IFN-β1a [87]. In fact, increased ALT was a more frequent cause of treatment discontinuation in patients on interferon than those on teriflunomide. These elevations occurred mostly in the first year of treatment. Thus the guidelines recommend monthly hepatic enzyme assessments for the first six months (every six months thereafter) and treatment should be discontinued with persistent elevations ≥ 3 times ULN.

The teratogenic effects of leflunomide noted in animal studies led to teriflunomide being the only MS medication that is pregnancy category X. However, in teriflunomide clinical trials, 83 pregnancies in female patients and 22 partners of male patients were reported [89]. The female patients had 26 live births, 29 induced abortions, and 13 spontaneous abortions. The partners of male patients had 16 live births, 2 induced abortions, and 1 spontaneous abortion, all without structural or functional defects. Despite this data, the medication continues to be category X and should be used with caution in women of child bearing potential. Thus, the recommendation remains for patients to use appropriate contraception and to undergo accelerated elimination should pregnancy be detected. The accelerated elimination with the use of cholestyramine (8 g three times daily for 11 days) or activated charcoal (50 g twice daily for 11 days) removes >98% of the plasma concentrations of teriflunomide [90].

Other adverse effects noted in the trials include diarrhea (16.3%), nausea (11.3%), alopecia (11.7%), upper respiratory infections (25.8%), headache, paresthesia, back and limb pains, and arthralgia. Mild to moderate hair thinning or loss was reported in the trials (14.6% in teriflunomide 14 mg vs 4.5% in placebo), but was not a cause of treatment discontinuation. The effects were transient as it resolved in most patients within 3–6 months while on treatment [91]. One patient in the TEMSO trial developed intestinal tuberculosis and another had cytomegalovirus hepatitis, hence patients starting teriflunomide should be screened with a tuberculin skin test or interferon gamma release assays.

8. DIMETHYL FUMARATE

Fumaric acid esters have been used in Germany for the treatment of psoriasis since 1994 under the brand name Fumaderm® [92, 93]. Fumaderm has been shown to induce T-helper 2 cytokines, induce activated T-cell apoptosis, and down-regulate intracellular adhesion molecules ICAM and VCAM in the CNS [94–96]. These mechanisms are thought in influence the pathogenesis of MS via impaired cellular proliferation and migration across endothelial barriers. In an open-label study, Fumaderm was shown to decrease gadolinium-enhancing lesions and decrease lymphocyte count [97]. Dimethyl fumarate (DMF) activates nuclear 1 factor (erythroid-derived 2)–like 2 (Nrf2), which is involved in protection of oligodendrocytes, myelin, axons and neurons [98]. DMF was approved for multiple sclerosis based the results of two phase 3 trials, DEFINE and CONFIRM [99, 100].

The most common adverse events associated with dimethyl fumarate are flushing, diarrhea, nausea, upper abdominal pain, upper respiratory tract infections, and erythema [99, 100]. Although flushing and gastrointestinal effects occurred mostly in the first 4–6 weeks and improved thereafter, both were a frequent cause of discontinuation [100]. Flushing, which occurred in about 30% of patients in the phase 3 trials was more persistent, but can be

mitigated with the use of aspirin (ASA) 325 mg 30 minutes prior to DMF intake [101]. No treatment has been proven to be effective at improving abdominal pain, although intake with food may reduce that effect [102]. Anecdotally, use of antacids, proton pump inhibitors, or H2-blockers have only partial benefit. Reports however, suggest intake with food high in fat content (peanut butter, chocolate milk, olive oil, almonds, cashews, potato chips, or avocados) may decrease GI side effects [103]. Some centers recommend a slower titration schedule than that designed by the manufacturing company. One group suggests taking the 120 mg dose twice daily for the first two weeks, followed by 240 mg dose with the largest meal and 120 mg with the opposite meal for weeks 3–4, then transition to 240 mg twice daily (with meals) [103]. Another group recommends taking 120 mg once daily for the first two weeks, then 240 mg once daily for weeks 3–4, then 240 mg twice daily (all doses with meals). A recent study investigated pretreatment with ASA 325 mg for mitigation of flushing as well as a slower titration schedule for the abdominal pain [104]. They started patients on 120 mg daily dosing for week 1, 120 mg twice daily for week 2, 240 mg and 120 mg for week 3, then 240 mg twice daily for week 4 onwards. While pretreatment with ASA decreased the incidence of flushing, the occurrence of abdominal change did not improve with the slower titration.

In the phase 3 trials, DMF-related lymphocyte reduction was 10% to 30%, and mostly occurred within the first year of treatment. Approximately 5% of patients had lymphocyte counts less than 500 cells/mm^2. There were no serious or opportunistic infections that were noted in patients on DMF within the trials. As of April 2015, six patients on fumaric acid preparations developed PML [105–109]. Five of these cases occurred in non-MS immune diseases and most were in the setting of either severe prolonged lymphocytopenia or prior immune suppressive therapy. The most recent case of PML in a patient on DMF for psoriasis occurred July 2014 [105]. This was not associated with lymphocytopenia. However, in October 2014, the first case of DMF-related PML occurred in a patient with MS, published in April 2015 [109]. The patient was enrolled in the DEFINE trial and was randomized to placebo, then transitioned to DMF for 4.5 years in the extension study. Within twelve months into therapy, she developed lymphocytopenia (lymphocyte count of 290 to 580 cells/mm^2) that persisted for 3.5 years. A relapse was suspected after she had severe gait and speech impairment with left arm incoordination, but failed to improve after administration of intravenous methylprednisolone and plasmapharesis. MRI and CSF JCV polymerase chain reaction were consistent with PML. A second (albeit nonfatal) case of DMF-associated PML in the setting of lymphocytopenia was reported by the company on July 16, 2015. While DMF has been shown to cause lymphocytopenia, a risk factor for the development of PML, lymphocytopenia may not be the only precipitating factor as previous cases in other diseases have indicated. Despite that, the current recommendations include monitoring lymphocyte counts every six months with consideration for discontinuing therapy should persistent lymphocytopenia occur (<500 cells/mm^2) [102]. At our center, if lymphocyte counts drop below 750 cells/mm^2, CBC is repeated every 3 months until the level rises above 750 cells/mm^2 [103]. If lymphocytes decrease to <500 cells/mm^2, CBC is checked monthly and JCV serology is obtained. Alternative therapy is considered with persistent lymphocytopenia and seropositive JCV.

9. ALEMTUZUMAB

Alemtuzumab is a humanized monoclonal antibody that depletes T and B-lymphocytes, monocytes, and eosinophils via targeting CD52 [110]. Within 12 months of treatment, lymphocyte counts are repleted to about 50% or the original level [111]. Monocytes return to baseline within one month, B-lymphocytes within three months, and T-lymphocytes within 12 months. In 2013, alemtuzumab was approved in Europe, Latin America, and Australia for active relapsing MS based on two phase 3 trials [113, 114]. In Canada, it is approved as a second-line agent [115]. The FDA initially declined approval for the medication due to risk of serious adverse effects, which will be discussed below. However, this decision was then reversed in November 2014 with an approved indication for relapsing MS patients who have failed two agents [116].

Alemtuzumab is administered as a daily four-hour infusion over two treatment courses: the first is over five consecutive days; the second is 12 months later, over three days [117]. Infusion reactions occur in over 90% of patients, most commonly include rash, headache, pyrexia, fatigue, pruritus, and nausea [112–114]. They are most common in the first day of the first course, and 3% of reactions may be severe. Premedication with IV methylprednisolone 1000 mg for the first 3 days (or prior to all infusions), in addition to antihistamine and antipyretic use may mitigate infusion reactions [117, 118].

Up to 5 years post infusion, novel autoimmune diseases have been shown to occur. It is hypothesized that this autoimmunity is related to repletion of B-lymphocytes faster than T-cell populations [119]. Thyroid autoimmune diseases are most common (34%), and can range from hyper- or hypothyroidism to a goiter. Standard thyroid disease treatment tends to be effective. A baseline thyroid stimulating hormone (TSH) level is recommended, along with rechecks every three months until 48 months after the last infusion (year 5 for those only receiving the initial two doses) [117, 118]. The risk of immune thrombocytopenia in patients on alemtuzumab is about 2% and was a cause of death in one of two deaths in the CAMMS223 trial [112]. Baseline CBC and diligent monthly rechecks should be performed. Patients should be educated regarding the symptoms and signs of thrombocytopenia such as easy bruising, petechiae, heavy menstruation, and hematoma development. Anti-glomerular basement membrane and membranous glomerulonephritis may rarely occur (0.3%), but can be severe. Prescribing information for alemtuzumab recommends baseline creatinine and urinalysis with urine cell counts at monthly intervals thereafter. Referral to nephrology should be initiated urgently if a concern is raised, as it is often difficult to determine the etiology of abnormalities since urinary tract infections (UTI) and hematuria are common in MS patients.

Infections after treatment with alemtuzumab are common (70%), and are serious in only 3% of patients [117]. Common infections include respiratory tract infections, UTIs, herpes viral infections, and influenza [112–114]. Herpes virus infections occurred in 16% of patients in the clinical trials (oral herpes 8.8%, herpes zoster 4.2%, herpes simplex 1.8%, genital herpes 1.3%) and serious herpetic infections were <0.2%. We recommend checking VZV IgG titers at baseline, with 2-dose varicella vaccination in VZV seronegative patients six weeks prior to alemtuzumab infusion [118]. Patients should also be on acyclovir for prophylaxis during

the first two months post infusion or until CD4 lymphocytes are >200 cells/μL. However, 80% of patients may not reach CD4 counts >200 cells/μL until 12 months post infusion, thus patients will likely need to be on prophylaxis for the first 24 months [120]. Annual human papilloma virus (HPV) screening is recommended given the 2% risk of HPV infections and cervical dysplasia in the trials. Active and latent tuberculosis have also been noted in 0.3% of patients on alemtuzumab in the trials. Prescribing information recommends screening with treatment of positive patients prior to infusion, especially in endemic areas. Fungal infections such as vaginal candidiasis and listeria meningitis have been reported as well.

The most common malignancies noted in patients on alemtuzumab were thyroid papillary carcinoma (0.3%) and melanoma (0.3%) [117, 121]. Baseline and annual dermatologic examinations should be performed. Patients should also be screened for thyroid cancer via routine neck examinations and be asked to monitor for any changes in their voice, hoarseness, dysphagia, or persistent unexplained coughing. Lymphoproliferative malignancies such as lymphoma, Castleman's disease, and a non-Epstein Barr Virus-associated Burkitt's lymphoma occurred in clinical trials, however the overall rate of malignancy was similar to control arms.

10. TREATMENT DECISIONS AND DMT SELECTION

Selection of DMT should be a joint decision between physicians and patients. Factors to consider in the decision making include: the patient's age, gender, comorbidities, viral exposure, prior or concurrent medications, previous DMT, severity and stage of their MS, adherence to therapy, and their preference. Younger patients (especially females) of childbearing age should lean towards medications with better pregnancy safety profiles than others. As discussed previously, physicians should avoid certain DMT in specific comorbidities; examples would be IFN-β in depression, fingolimod in cardiac disease, DMF in irritable bowel disease, teriflunomide in liver failure, etc. Previous immunosuppressive medications should raise concern when natalizumab is considered. Patients on medications that alter cardiac conduction may need to suspend their medications prior to fingolimod's first-dose administration. Keeping in mind the various efficacy profiles for the DMT, disease activity as measured by clinical relapses, MRI lesion burden, and disability progression should heavily influence the decision-making as well [122]. Some medications require strict monitoring, as is the case in alemtuzumab, which requires routine monitoring for five years. Hence, it may not be an appropriate choice in noncompliant patients. Finally, some patients have reservations regarding injection medications as opposed to oral ones; others prefer those with extensive safety data.

Typically, injectable DMT are considered to have similar efficacies [10, 123–125]. Their extensive safety data makes them obvious first-line agents. Selection among them involves consideration for administration frequency and adverse effect tolerance. Oral agents have performed equally or superior to injection medications in phase 3 trials [62, 99, 87]. However their adverse effects tend to be greater. As such, they are viewed as either first- or second-line therapies. Natalizumab is also considered a first- or second-line agent depending on the disease activity, but its use is more dependent on the patient's JCV status. Alemtuzumab should be considered in active disease that is refractory to two agents, and as

mentioned previously, it requires strict adherence to routine monitoring. If therapy is being switched due to intolerance, then the next agent should typically be of equal or stronger efficacy. If it is due to breakthrough disease, then a more efficacious agent with a higher likelihood for disease control should be considered.

In addition to the discussion on DMT selection, clinicians should discuss and educate patients about the risk of not treating MS. Natural history studies have shown that MS relapses produce measurable effects on disability [126–128]. Data from clinical trials have shown that patients who delay treatment initiation, or those previously on placebo who transition to active arms, do not achieve the same disease control as those started on active therapies earlier in their course [65, 129–131]. Discussions regarding DMT use in progressive MS are equally important. Several phase 2 and 3 trials have evaluated therapies in progressive MS [132]. Although no trial has clearly shown positive results, cohorts within the trials that have done well had some evidence for ongoing inflammation. Thus it may be worth maintaining patients on active therapy if signs of disease activity are present.

11. CONCLUSION

The current thirteen approved DMT have shown various efficacy and adverse effect profiles. The older agents have had a long safety track record, but relatively modest efficacy. Newer oral and infusion therapies are much more robust in their disease control, however these agents are associated with higher risk of adverse events and the complete safety profile is not fully determined for some. These facts should always be taken into consideration when discussing therapy options with patients. With the exception of mitoxantrone and alemtuzumab, these agents are all approved for relapsing forms of MS and may be considered as first line therapy in the correct setting. With regards to the risk of PML in the newer agents, much is yet to be learned and uncovered. However, it is possible that PML may be a risk with any of the agents especially when taking into account history of DMT. Careful selection of medication after consideration of risk benefit relation should be made with the physician and patient together. Appropriate monitoring and safety plans should be continuously updated as our understanding of side effects improves.

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KEY POINTS

- As of April 2015, thirteen disease-modifying therapies are approved. Seven are injectable, three are oral, and three are infusion-based.
- The older agents have a long safety record but modest efficacy, the newer agents are much more robust in disease control but carry significant adverse effects.
- Treatment decisions should be a joint effort between the patient and physician. An individualized approach with careful risk stratification and mitigation is necessary.

Table 1

Recommended baseline and routine testing for disease modifying agents

Disease Modifying Agent	Baseline testing	Routine monitoring
Interferon-beta or pegylated interferon	• CBC • LFT	• CBC and LFT at month 1, 3, 6 then every 6 to 12 months Thyroid function tests
Glatiramer acetate	• None	• None
Mitoxantrone	• CBC • LFT • EKG • Echocardiogram or MUGA	• CBC, LFT, and uric acid levels prior to each infusion • Echocardiogram or MUGA prior to each infusion • Annual echocardiogram or MUGA post discontinuation
Natalizumab	• LFT • JCV Ab	• LFT at month 3 and 6 then every 6 months • JCV Ab every 6 months • Natalizumab Ab at 6 months
Fingolimod	• CBC • LFT • VZV IgG • EKG • Eye exam or OCT • PFT if respiratory symptoms • Consider skin exam	• LFT at month 3 and 6 then every 6 months • Eye exam or OCT at month 3 • PFT if respiratory symptoms • Consider Skin exam
Teriflunomide	• CBC • LFT • Bilirubin • PPD or QFT-G	• LFT monthly for 6 months then every 6 months • CBC every 6 months
Dimethyl fumarate	• CBC	• CBC every 6 months (every 3 months if lymphocytes <750 or every month if <500) • JCV Ab if lymphocytes <500
Alemtuzumab	• CBC • Cr • UA (with cells), • TSH, • Skin exam	• CBC, Cr, UA (with cells) monthly • TSH every 3 month • Skin exam annually

Ab = antibodies; CBC = complete blood count; Cr = creatinine; EKG = electrocardiogram; IgG = immunoglogulin G;; JCV = John Cunningham virus; LFT = liver function test; MUGA = multigated acquisition scan OCT = ocular coherence tomography; PFT = pulmonary function test; PPD = purified protein derivative; QFT-G = QuantiFERON ® gold test; TSH = thyroid stimulating hormone UA = urinalysis; VZV = varicella zoster virus.

Table 2

Adverse effect or risk mitigation strategies for the disease modifying therapies

Disease Modifying Agent	Adverse effect or risk	Mitigation
Interferon-beta	• Flu-like symptoms • Injection site reactions • Depression	• NSAIDs or acetaminophen, hydration. • Applying ice to the site prior to injection, site rotation, and proper injection techniques. Screen and monitor for depression, suicidal ideation
Glatiramer acetate	• Injection site reactions • Immediate post-injection systemic reaction	• Applying ice to the site prior to injection, site rotation, and proper injection techniques
Mitoxantrone	• Congestive heart failure, • Secondary AML, • Amenorrhea	• Limit dosing to a cumulative 140 mg/m2 (approximatei 10 courses). • Monitor blood counts after 60 mg/m2
Natalizumab	• PML Hypersensitivity reactions • Infusion reactions	• Stratify PML risk by JCV Ab status, prior immune suppression, and duration of therapy • Pretreat with loratadine and acetaminophen • Routine anti-natalizumab antibody testing and MRI brain especially if neurologic symptoms arise or worsen
Fingolimod	• First-dose cardiac events (bradycardia, AV block, cardiac arrest, arrhythmias) • Herpes infection • Macular edema • PML • Headaches	• First-dose observation for 6 hours with hourly heart rate and blood pressure measurements. • Vaccination with varicella vaccine if VZV IgG negative. • Acyclovir for herpetic infections. • Eye exams or OCT for edema. Patients to monitor for metamorphopsia. • No current guidelines for PML. Patients however should be aware of PML symptoms
Teriflunomide	• Teratogenesis • Liver toxicity • Reactivation of latent tuberculosis	• Ensure proper contraception for both male and female patients • Contraindication for existing liver disease or TB exposure. • Accelerated elimination via cholestyramine (8 g three times daily for 11 days) or activated charcoal (50 g twice daily for 11 days)
Dimethyl fumarate	• Flushing • GI: Abdominal pain, diarrhea, nausea • PML	• Aspirin 325 mg 30 minutes prior. • Intake with full stomach, may also consider food with fat content peanut butter, chocolate milk, olive oil, almonds, cashews, potato chips, or avocados. • Monitor lymphocyte counts routinely, check JVC Ab if <500
Alemtuzumab	• Infusion reactions • Infections • Autoantibody disorders (thyroid, ITP, anti-GBM disease)	• Pretreatment with methylprednisolone 1000 mg antipyretics, and antihistamines • Clinical monitoring for UTI, URI • Acyclovir prophylaxis for herpetic infection

Disease Modifying Agent	Adverse effect or risk	Mitigation
	• Cancers (thyroid, melanoma)	

Ab = antibodies; AML = acute myelogenous leukemia; AV = atrioventricular; GBM = glomerular basement membrane; GI = gastrointestinal; ITP = idiopathic thrombocytopenic purpura; JCV = John Cunningham virus; NSAIDs = nonsteroidal anti-inflammatory drugs; OCT = optical coherence tomography; TB = tuberculosis; URI = upper respiratory tract infections; UTI = urinary tract infections; VZV = varicella zoster virus.