Update on monitoring and adverse effects of approved second-generation disease-modifying therapies in relapsing forms of multiple sclerosis

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Purpose of review
There has been a considerable increase in the number of disease-modifying therapies (DMTs) in recent years. It appears that the number of approved DMTs is going to continue to increase in the coming years. The growing number of DMTs has provided a challenge to the clinician to tailor their therapeutic recommendations based on patients’ needs and preferences. To choose between these DMTs, knowledge of side-effect profiles is imperative.

Recent findings
Alemtuzumab, a humanized recombinant monoclonal antibody, was recently approved for the management of relapsing forms of multiple sclerosis. Its use seems to be limited by significant adverse effects and regular monitoring requirement. In 2014, the first case of progressive multifocal leukoencephalopathy (PML) was diagnosed in a patient with relapsing remitting multiple sclerosis who received extended dimethyl fumarate without any significant confounding factors. Among patients receiving fingolimod after previous natalizumab treatment, there have been 17 suspected cases of PML. There have also been three confirmed cases of PML in individuals who received fingolimod without previous natalizumab treatment.

Summary
In this review, we outline the potential adverse effects and recommended laboratory studies as part of the monitoring strategy following initiation of various DMTs.

Keywords
adverse effects, disease-modifying therapy, drug monitoring, multiple sclerosis

INTRODUCTION
Over the last two decades, there has been a considerable increase in the number of disease-modifying therapies (DMTs). Currently, there are 13 US Food and Drug Administration (FDA)-approved medications for management of relapsing forms of multiple sclerosis (MS) [1]. Additional agents will very likely be approved in the next few years (including daclizumab and ocrelizumab) [2]. To choose between these DMTs, knowledge of side-effect profiles is imperative. In this review, we outline the potential adverse effects and recommended laboratory studies as part of the monitoring strategy following initiation of various DMTs.

TERIFLUNOMIDE
Teriflunomide, introduced in 2012, is a DMT which can be taken orally and is approved for the treatment of relapsing remitting MS [3]. Teriflunomide, most commonly causes gastrointestinal (GI) disturbances, including oral ulcers, nausea, vomiting, indigestion, and diarrhea (Table 1) [4–8]. These side-effects are usually most pronounced with initiation of therapy and resolve after about 2 weeks.

Teriflunomide can cause hepatotoxicity, including fatal liver failure, and should not be taken by patients with preexisting liver disease or by those who have alanine amino transferase (ALT) at least 2 times the normal range.
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KEY POINTS

- Therapeutic options for relapsing forms of MS have expanded in recent years.
- Newer drugs are more efficacious, but have been associated with more severe potential adverse effects.
- Stringent monitoring is required to avoid or detect these adverse effects early.
- Selection of appropriate DMT in pregnancy is a challenge for the physician.
- Understanding of adverse effects of these newer medications may enhance our understanding of human autoimmune disease.

The medication can lead to a mild increase in blood pressure and therefore one should measure the patients’ blood pressure before initiating therapy and periodically thereafter [7,13–15].

Teriflunomide is contraindicated in pregnant women [10]. It has been assigned pregnancy category X. A pregnancy test prior to initiation is required. In the case of pregnancy, treatment with teriflunomide should be terminated immediately and an accelerated elimination procedure (discussed above) should be initiated.

DIMETHYL FUMARATE

Dimethyl fumarate (DMF) was approved by the FDA in March 2013 [16]. Since then, there has been an exponential increase in its use as a first-line DMT.

Use of fumaric acid esters (FAE) for management of psoriasis for many decades helped in establishing its long-term safety [17]. In over 30000 patient years, flushing and GI symptoms have been reported as the most common adverse effects [18]. Flushing and GI side-effects diminished in frequency and intensity with continued FAE use.

Even among MS patients, flushing and GI events continued to be the most common adverse effects [19]. The mechanism of action for flushing is prostaglandin release [20]. Therefore, pretreatment with prostaglandin inhibitors such as aspirin may reduce the incidence and severity of flushing. Use of aspirin has not shown any significant benefit in reduction of GI side-effects.

Elevation of transaminases to three times of baseline was detected in 6% of patients receiving oral DMF compared with 3% of patients receiving placebo [21,22]. No opportunistic infections were reported in the two phase III trials.

To date, among patients with psoriasis on FAE, four cases of PML have been reported [23–27]. Two of these patients had severe lymphocytopenia most likely because of FAE use and the remaining two patients had confounding, known PML risk factors, such as history of sarcoidosis, underlying malignancy, and use of other immunosuppressive agents, including methotrexate and efalizumab [28]. In 2014, the first PML case in a patient with MS who had been treated with extended release DMF for 4.5 years was reported [29**]. One year after initiation of DMF the patient had developed severe lymphocytopenia (lymphocyte count, 290–580 cells/mm³) which persisted for 3.5 years. The patient subsequently died of complications from pneumonia.

In the phase III trial, significant lymphopenia was reported in 4% thrice-daily DMF, 5% in twice-daily DMF, and less than 1% in placebo group [21,22]. Therefore, monitoring of lymphocyte...
<table>
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<th>Drugs</th>
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<td>Teriflunomide</td>
<td>Potent inhibitor of dihydroorotate dehydrogenase which is needed for T- and B-cell proliferation</td>
<td>7 or 14 mg daily (p.o.)</td>
<td>GI disturbances, hepatotoxicity, lymphopenia, thrombocytopenia, high blood pressure, opportunistic infections, potentially teratogenic</td>
<td>Liver studies, complete blood counts, blood pressure, tuberculosis testing, pregnancy test</td>
<td>X</td>
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<td>Dimethyl fumarate</td>
<td>Increase expression of anti-inflammatory cytokines and decrease expression of proinflammatory cytokines, increased production of reduced glutathione</td>
<td>120 mg b.i.d. for 1 week, then 240 mg b.i.d. (p.o.)</td>
<td>Flushing, diarrhea, nausea, vomiting, lymphopenia</td>
<td>White blood cell count</td>
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<td>Fingolimod</td>
<td>Decreased egress of lymphocytes from the lymph nodes</td>
<td>0.5 mg daily (p.o.)</td>
<td>Bradyarrhythmias, macular edema, hepatic transaminits, Basal cell carcinomas, herpes encephalitis</td>
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<td>Natalizumab</td>
<td>α4 integrin antagonist, prevents leukocyte migration. Modulates priming, and activation of leukocytes in brain, induces apoptosis via interaction with fibronectin</td>
<td>300 mg every 4 weeks (IV)</td>
<td>Infusion reaction, PML, melanoma, liver disease, fever, joint pain</td>
<td>JC virus antibodies, liver enzymes</td>
<td>C</td>
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<tr>
<td>Alemtuzumab</td>
<td>Depletion of CD52+ immune cells by ADCC and CDC and apoptosis</td>
<td>12 mg daily for 5 days, 12 months later 12 mg daily for 3 days (IV)</td>
<td>Infusion reaction, autoimmune disorders (thyroid dysfunction, ITP, glomerulonephritis)</td>
<td>White blood cell count, platelet count, thyroid-stimulating hormone, liver enzymes, pregnancy test</td>
<td>C</td>
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ADCC, antibody-dependent cell-mediated cytotoxicity; b.i.d., twice a day; CDC, complement-dependent cytotoxicity; EKG, electrocardiogram; GI, gastrointestinal; ITP, immune thrombocytopenic purpura; IV, intravenous; PML, progressive multifocal leukoencephalopathy; p.o., orally. Interpretation: Pregnancy category B – well controlled trials revealed no risk, whereas animal trials have shown adverse effects or no well controlled trials, but animal trials revealed no increased risk. Pregnancy category C – animal studies have not been conducted or have shown increased risk for the fetus; no well controlled trials in pregnant women. Pregnancy category D – studies have shown harm to the fetus, however, the benefit may outweigh risk under certain circumstances. Pregnancy category X – studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse effect data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
counts in patients on DMF and dose reduction or temporary discontinuation or change in DMA should be considered in cases of prolonged severe lymphopenia [19].

In experimental animal studies, fetal adverse effects were observed; therefore, it has been assigned pregnancy category C [10]. Based on postmarketing experience up till June 30, 2014, 63 pregnant patients receiving DMF have been reported in trials [30*]. Among 42 patients with known outcomes, 26 had live births (67%), three spontaneous abortions (8%), and 10 elective terminations (26%). The incidence of spontaneous abortion was consistent with the expected rate of early ‘pregnancy’ loss in the general population.

NATALIZUMAB

Natalizumab is a humanized monoclonal antibody directed against the α4 subunit of α4β1 and α4β7 integrin molecules [2].

Common adverse effects reported in the group receiving natalizumab in the phase III trial (AFFIRM: Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) were fatigue and hypersensitivity reactions (allergic dermatitis, urticaria, anaphylactic reaction) [31]. As most of these allergic reactions occur soon after infusion, postinfusion observation for 1 h is recommended. The most well known and feared adverse effect associated with natalizumab is the development of PML [32]. So far, more than 600 cases of PML have been reported in association with natalizumab administration. Various risk factors have been identified to be associated with increased risk of developing PML, including a positive John Cunningham Virus serology, natalizumab administration for more than 2 years and prior use of immunosuppressive agents [32,33]. Despite the identification of these risk factors, the incidence of PML among patients receiving natalizumab therapy has not changed [34*].

The risk management initiative known as the Tysabri Outreach Unified Commitment to Health (TOUCH) program was started to improve detection of signs of symptoms suggestive to PML [35]. As part of the TOUCH program, patients are questioned about symptoms, such as visual changes, speech changes, subacutely worsening of motor, or sensory symptoms before each natalizumab infusion [2,10]. Currently, the standard approach to manage PML related to natalizumab infusion is to discontinue the infusion and institute plasmapheresis to remove the monoclonal antibody from the circulation to reintroduce CNS immunosurveillance [36].

Other side-effects include development of malignancy [37,38]. There was higher reported incidence of malignancy in the natalizumab arm including three breast cancers, one cervical cancer, and one metastatic melanoma. Neutralizing antibodies were detected in 9% of patients. There was also a higher incidence of hepatic transaminitis [31]. Therefore, it is recommended to test liver enzymes prior to initiation of treatment and at 1 month and 3 months after initiation of therapy. Complete blood counts should also be determined at 1, 3, and 6 months after initiation and every 6 months thereafter.

Animal studies have shown higher rate of abortion at high doses (7 times the human dose) [10,35]. Therefore, natalizumab has been assigned a pregnancy category C. Discontinuation of therapy during pregnancy presents its own challenges, as there is no ideal alternative therapy which is well tolerated in pregnancy and will prevent disease reactivation after cessation of natalizumab infusion.

FINGOLIMOD

Fingolimod is a sphingosine-1-phosphate receptor modulator which prevents egress of naïve and central memory T cells from the lymph nodes and thymus [39].

Common side-effects associated with fingolimod in the FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis) trial were headache, back pain, flu like symptoms, diarrhea, back pain, cough, bronchitis, depression, sinusitis, dizziness, and elevated liver enzymes [40,41]. More severe adverse effects include bradycardia, MS relapse, macular edema, and basal cell carcinoma [42]. One death in the fingolimod arm of the trial was secondary to suicide.

Cardiac complications associated with fingolimod include transient reduction of heart rate after initiation [42,43]. This is considered to be secondary to hyperpolarization of atrial myocytes because of sphingosine-1-phosphate receptor-mediated activation of inward rectifying potassium channel. Maximal reduction occurs in the first 6 h of the first dose. The incidence and extent of reduction of heart rates is considerably less with the second dose. At the recommended dose of 0.5 mg per day the mean reduction is 12–13 beats/min [42,44]. In clinical studies, the incidence of bradycardia was higher in the 1.25 mg/day dosing group compared with 0.5 mg/day group [10,42]. Second-degree Mobitz type-1 atrioventricular (AV) block occurred in 1% of patients receiving 1.25 mg/day dose of fingolimod and only in less than 0.2% of patients receiving 0.5 mg/day dose, whereas 2:1 AV block occurred in 0.2% and 0 in the corresponding groups [45].
During postmarketing surveillance, cases of transient asystole and unexplained death have occurred within 24 h of initiation of fingolimod [46]; preexisting disease or use of other medications were present in these patients and it is unclear whether fingolimod was causally related to these events [47]. Instances of syncope after the first dose of fingolimod have also been reported [42]. The FDA and European Medicines Agency (EMA) have recommended 6-h heart monitoring with continuous electrocardiogram monitoring during the first administration of fingolimod. If bradycardia occurs within the first 6 h, cardiac monitoring should be extended for another 2 h. Any episodes of severe bradycardia, corrected QT interval prolongation, AV block type II Wenckeback, or AV block type III requires overnight observation. During the course of therapy if the treatment is held for 14 days or more, cardiac monitoring has to be repeated. As per EMA recommendation if there is interruption in therapy for 1 day during first week or for 7 days during 3rd and 4th week cardiac monitoring should be repeated [46]. Cardiology evaluation is warranted in patients who develop bradycardias while on fingolimod or patients who are concurrently taking other agents which promote bradycardia to determine the feasibility of fingolimod therapy.

Macular edema is another severe adverse effect; this may lead to progressive visual loss [10,42]. The pathogenesis of macular edema in association with fingolimod remains unclear. In the pooled analysis of FREEDOMS and TRANSFORMS (Trial Assessing Injectable Interferon vs. FTY720 Oral in Relapsing Remitting Multiple Sclerosis) trial, macular edema occurred in 19 cases [10,40,41]. Fifteen of these cases were in 1.25 mg/day dose, whereas four of these cases were in 0.5 mg/day dose. In 64% of cases, macular edema occurred within 3–4 months of initiation of fingolimod. The majority of patients (84%) had resolution of macular edema when fingolimod was stopped with a small subset receiving topical anti-inflammatory medications for complete recovery [48]. None of the patients had progressive macular changes after discontinuation of the fingolimod. The incidence of macular edema seems to be low (0.3%) in the currently approved dose (0.5 mg/day) of fingolimod [42]. Cases of lymphomas, basal cell, and melanomas (in situ) have also been reported [42,51]. A dermatology screening examination should be suggested before the initiation of fingolimod therapy.

In the FREEDOMS II trial, herpes virus infection occurred in 10% of patients receiving 1.25 mg/day dose and 8% patients receiving 0.5 mg/day dose of fingolimod compared to only 5% cases of placebo [42,51]. In the TRANSFORMS trial, 5.5% of the 1.25 mg/day fingolimod recipients, 2.1% of the 0.5 mg/day fingolimod recipients, and 2.8% of the interferon (IFN)-β1a recipients developed herpes virus infection [40]. One patient who was on fingolimod for approximately 10 months developed disseminated herpes virus infection while receiving corticosteroids and died from its complications. Another patient who received corticosteroids for suspected MS relapse, developed herpes simplex virus 1 encephalitis and died despite treatment with antiviral therapy. All these patients were treated with the higher, nonapproved 1.25 mg dose [42].

It is recommended that the patients without history of chicken pox or who have not received varicella zoster virus (VZV) vaccination should be checked for antibodies against VZV [52]. If the antibodies are negative, VZV vaccination should be administered before initiation of fingolimod.

It is estimated that approximately 20,000 individuals have received fingolimod after previous natalizumab treatment. Among these patients, there have been 17 suspected cases of PML [53**]. There have also been three confirmed cases of PML in individuals who received fingolimod without previous natalizumab treatment. Because of the risk of PML, it is recommended that fingolimod be held if there is clinical suspicion of PML and an MRI be considered.

Fingolimod has been assigned pregnancy category C, based on data from animal studies which have shown evidence of teratogenicity and embryolethality [47]. If a patient becomes pregnant, the administration of fingolimod should be terminated [47,49].

**ALEMTUZUMAB**

Alemtuzumab is a humanized recombinant monoclonal antibody against CD52 recently approved by the US FDA and the EMA for the management of relapsing forms of MS [54].

Infusion reaction has been reported to be the most common adverse effect, occurring in 90–99% of patients [55,56]. These reactions are characterized by fever, fatigue, nausea, headache, rash, and pruritus. Transient worsening of preexisting...
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neurological deficits during infusion probably because of release of cytokines has also been observed.

Mild-to-moderate infections involving upper respiratory tract or urinary tract were also common occurring in 77% of patients treated with alemtuzumab [55,56]. There was a relatively high incidence (16%) of herpes infections in alemtuzumab-treated patients, which was alleviated by prophylactic treatment with acyclovir. Rare infections because of immunosuppression which have been reported in the open-label trials include: spirochetal gingivitis, pyogenic granuloma, and listeria meningitis [54,57]. Cases of PML have not been reported so far. Preservation of innate immune system and sparing of memory T-cells and memory B-cells has been proposed as the potential mechanism for low rate of opportunistic infections [54,57,58].

A major concern with infusion of alemtuzumab has been an increased risk of autoimmunity. Autoimmune thyroiditis has been reported in approximately 30% of alemtuzumab-treated patients in the phase III trials [55–57]. In the CAMMS223 (A Phase II Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Rebif® in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis) 5-year follow-up study, thyroid dysfunction was seen in 39 and 29% of patients treated with alemtuzumab 12 and 24 mg, respectively [59]. The rate is as high as 41% in long-term studies. Onset of thyroid autoimmunity ranges from 6 to 61 months after initiation of alemtuzumab treatment, suggesting a potential link with repopulation of lymphocytes [56–60].

Immune-mediated thrombocytopenia (ITP) was seen at higher frequency in alemtuzumab-treated group compared with the IFN-β1a-treated group [55,56,60]. The rate of ITP was ~1% in (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis I) and (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis II). It was even higher (3.5%) in the Cambridge long-term study [61]. Seven patients were diagnosed with ITP in CAMMS223 [59]. Six were in alemtuzumab-treatment group, whereas one was in the IFN-β1a-treatment group. In June 2005, one of the six patients died secondary to intracranial hemorrhage. ITP associated with alemtuzumab typically is delayed (median 24.5 months) following initial drug administration [62]. This delay may point towards the potential role of lymphocyte repopulation in the manifestation of ITP.

Alemtuzumab has also been associated with the development of glomerulonephritis [57]. Two patients developed antiglomerular basement membrane (anti-GBM) disease and had to undergo renal transplantation [63]. Four cases of glomerulonephritis associated with alemtuzumab infusion (0.3%) were reported in the phase II and phase III trials (CAMMS223 and CARE MS), including two cases of membranous glomerulonephritis and two cases of antiglomerular basement membrane disease [55–57,59,60].

Onset of alemtuzumab associated renal dysfunction ranges from 4 to 39 months [54,57,64]. Clinical manifestations may include elevation of serum creatinine, hematuria, and/or proteinuria. Owing to the above mentioned adverse effects, prescription of alemtuzumab has been restricted by Risk Evaluation and Mitigation Strategy (REMS) Program [65]. As part of a safety initiative, REMS Program requires not only the patients but also all physicians, pharmacies, healthcare pharmacies associated with prescriptions, and infusion of alemtuzumab to be enrolled. The protocol includes a monthly questionnaire for signs and symptoms of ITP offset by 2 weeks from the monthly laboratory monitoring, which has been recommended for the first 48 months [54,58] This includes monthly monitoring of serum creatinine, complete blood count with differential, urinalysis, and microscopy and 3-monthly monitoring of thyroid function test. Any detection of thrombocytopenia or worsening renal function (serum creatinine), unexplained hematuria, and/or proteinuria should prompt evaluation for ITP or possible glomerulonephritis. Patients are advised to continue safety monitoring for at least 4 years after their last dose.

Alemtuzumab can cross the blood placental barrier, therefore, it has potential to cause fetal adverse outcomes [10]. Currently, it has been assigned pregnancy category C by the US FDA.

CONCLUSION
More choices in pharmacotherapies have allowed neurologists to tailor treatments to specific patients and situations. Making the right treatment decisions requires knowledge of the efficacy and safety of specific agents. Continued research and collection of data are going to further help the clinicians in making well informed recommendation to prevent relapses and disease progression.

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Conflicts of interest
O.S. serves on the editorial boards of JAMA Neurology, Multiple Sclerosis Journal, and Therapeutic Advances in
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Neurological Disorders. He has served on data monitoring committees for Pfizer and Sanofi-Aventis without monetary compensation. He represented Novartis in front of a Scientific Advisory Group at the European Medicines Agency (EMA). He has advised Genentech and Sanofi-Aventis. He has consulted for Huron Life Sciences and Navigant Consulting. He currently receives grant support from Teva Pharmaceuticals and Opexa Therapeutics. He is funded by a Merit grant from the US Department of Veterans Affairs. The remaining authors have no conflict of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest


First case of progressive multifocal leukoencephalopathy in a patient with RRMS under DMF therapy.


Study of pregnancy outcomes in patients on DMF therapy.


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