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*AJNR Am J Neuroradiol* 2017, 38 (9) 1664-1671

doi: <https://doi.org/10.3174/ajnr.A5147>

<http://www.ajnr.org/content/38/9/1664>

This information is current as of August 9, 2025.

# Current and Emerging Therapies in Multiple Sclerosis: Implications for the Radiologist, Part 1—Mechanisms, Efficacy, and Safety

 C. McNamara,  G. Sugrue,  B. Murray, and  P.J. MacMahon



## ABSTRACT

**SUMMARY:** Imaging for the diagnosis and follow-up of patients with suspected or confirmed multiple sclerosis is a common scenario for many general radiologists and subspecialty neuroradiologists. The field of MS therapeutics has rapidly evolved with multiple new agents now being used in routine clinical practice. To provide an informed opinion in discussions concerning newer MS agents, radiologists must have a working understanding of the strengths and limitations of the various novel therapies. The role of imaging in MS has advanced beyond monitoring and surveillance of disease activity to include treatment complications. An understanding of the new generation of MS drugs in conjunction with the key role that MR imaging plays in the detection of disease progression, opportunistic infections, and drug-related adverse events is of vital importance to the radiologist and clinical physician alike. Radiologists are in a unique position to detect many of the described complications well in advance of clinical symptoms. Part 1 of this review outlines recent developments in the treatment of MS and discusses the published clinical data on the efficacy and safety of the currently approved and emerging therapies in this condition as they apply to the radiologist. Part 2 will cover pharmacovigilance and the role the neuroradiologist plays in monitoring patients for signs of opportunistic infection and/or disease progression.

**ABBREVIATIONS:** IFN $\beta$  = interferon  $\beta$ ; NTZ = natalizumab; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting MS

Multiple sclerosis is an idiopathic chronic inflammatory demyelinating disease of the central nervous system. The median age of symptomatic onset is approximately 29 years, and the female-to-male ratio in this group approaches 3:1.<sup>1</sup> The McDonald criteria were introduced in 2001 as guidelines to facilitate a timely and accurate diagnosis of MS.<sup>2</sup> These criteria have resulted in an earlier diagnosis of this condition with a high degree of both specificity and sensitivity, allowing earlier medical intervention.<sup>3</sup> In 2010, revisions to the McDonald criteria allowed, in some instances, a more rapid diagnosis of MS, with equivalent or improved specificity and/or sensitivity compared with past criteria and allowed the clarification and simplification of the diagnostic process with fewer MR imaging examinations required.<sup>3</sup> Central to these guidelines is the use of MR imaging and the need to demonstrate the dissemination of neurologic lesions in both time and space. As a result, the radiologist plays an increasingly central

role in the multidisciplinary team care of patients diagnosed with this disease.

During the past 10 years, there has been an evolution in the treatment of relapsing-remitting MS (RRMS), with a rapid increase in the number of disease-modifying therapies available (On-line Table ). Since 2004, 7 new agents have been approved by the US Food and Drug Administration for the treatment of the relapsing form of the disease, joining what had previously been the mainstay of MS treatments: interferon  $\beta$  (IFN $\beta$ ) and glatiramer acetate.<sup>4</sup>


The radiologist has a pivotal role in the diagnosis of MS, along with monitoring and identifying complications associated with these latest treatments. Part 1 of this review details recent developments in the treatment of MS and discusses the published clinical data on the efficacy and safety of the currently approved and emerging therapies in this condition as they apply to the radiologist. Part 2 focuses on the role of the neuroradiologist in monitoring patients being treated with these medications, which includes observation for treatment complications and signs of disease progression.


## Currently Approved Agents: First-Line Therapies

**Interferon  $\beta$ .** Interferon  $\beta$  is based on a naturally occurring polypeptide predominantly produced by fibroblasts. Its anti-inflam-

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<http://dx.doi.org/10.3174/ajnr.A5147>

matory effects are largely believed to result from the inhibition of T-lymphocyte proliferation.<sup>5</sup> It is administered by intramuscular or subcutaneous injection. Phase III trials of all the IFN $\beta$  preparations have reduced the annualized relapse rate by about 30%, reduced the progression of disability in RRMS, and reduced visible MR imaging disease activity.<sup>6–8</sup> Most patients treated with IFN $\beta$  (50%–75%) experience flulike symptoms, which usually resolve within 24 hours. Liver enzymes may become elevated, and bone marrow function may be depressed, which warrants periodic surveillance of liver function and blood counts before starting therapy and every 6 months thereafter.<sup>9–11</sup> Isolated cases of severe injection-site reactions involving infection or necrosis and severe cases of acute liver failure and pancreatitis have been reported.<sup>5</sup>

**Glatiramer Acetate.** Glatiramer acetate is a pool of synthetic peptides with an amino acid composition similar to that of myelin basic protein and has widespread effects on the innate and adaptive immune systems.<sup>12</sup> It is an immunomodulatory agent that does not affect the number of circulating lymphocytes but rather switches lymphocyte polarization from a proinflammatory TH<sub>1</sub> to an anti-inflammatory TH<sub>2</sub> profile.<sup>13</sup> Glatiramer acetate is administered by subcutaneous injection. Glatiramer acetate treatment trials in RRMS have shown a significant reduction in the annualized relapse rate (29%) and a reduction in gadolinium-enhancing MR imaging activity.<sup>14,15</sup> Glatiramer acetate is usually well-tolerated, but most patients (65%) experience injection-site reactions (pain, erythema, swelling, and pruritus). About 15% report a transient self-limited systemic reaction (immediately after injection) of facial flushing and chest tightness, accompanied at times by palpitations, anxiety, and dyspnea. Other reported adverse events include lymphadenopathy and lipotrophy.<sup>6,15,16</sup>

**Teriflunomide.** Teriflunomide (Aubagio), the active metabolite of leflunomide (an antirheumatic drug), is an oral disease-modifying therapy for RRMS, which was approved by the FDA in September 2012.<sup>17</sup> Teriflunomide reduces T- and B-cell activation, proliferation, and function in response to autoantigens by inhibiting a key mitochondrial enzyme involved in DNA replication. Teriflunomide significantly reduces relapse rates, disability progression, and MR imaging evidence of disease activity, compared with a placebo.<sup>18</sup> It showed a 31% reduction in the annualized relapse rate and a 30% reduction in disability compared with a placebo.<sup>19</sup> On MR imaging, teriflunomide was superior to a placebo in reducing the total lesion volume and the number of gadolinium-enhancing lesions.<sup>18</sup> While no radiologic-specific adverse events have been reported to date with teriflunomide, the most common clinical and biochemical adverse events include headache, diarrhea, fatigue, elevated alanine aminotransferase levels, nausea, hair thinning, influenza, and urinary tract infections.<sup>20</sup>

**Dimethyl Fumarate.** Dimethyl fumarate (Tecfidera) is an orally administered immunomodulatory agent with anti-inflammatory properties, and its mechanism of action in MS is only partially understood.<sup>5</sup> Two Phase III trials of RRMS showed that dimethyl fumarate, compared with a placebo, reduced the annualized relapse rate by 44%–53%, the rate of disability progression by 22%–

32%, and the number of gadolinium-enhancing lesions by about 75%–94%.<sup>21,22</sup> Common adverse events included flushing, nausea, diarrhea and abdominal pain, neutropenia, and elevated liver function test results.<sup>21,22</sup> Recently, a case of fatal progressive multifocal leukoencephalopathy (PML) was reported in a 54-year-old woman with MS who was treated with dimethyl fumarate.<sup>23</sup> Furthermore, 4 cases of PML have previously been described in patients with psoriasis who had received Fumaderm (related fumaric acid esters have been used in Europe since 1994 for the treatment of psoriasis).<sup>24</sup> Prolonged severe lymphopenia (<500 cells per cubic millimeter) that persists for >6 months has been suggested as a risk factor for PML in this patient cohort. Thus, Torkildsen et al<sup>5</sup> have recommended that in patients with persistent lymphopenia who are John Cunningham virus–positive, dimethyl fumarate treatment should be terminated.

### **Currently Approved Agents: Second-Line Therapies**

**Fingolimod.** Fingolimod (Gilenya), a sphingosine 1-phosphate receptor modulator, was the first oral disease-modifying therapy to be approved for the treatment of RRMS and is administered as a capsule taken once daily.<sup>25</sup> Fingolimod antagonizes the sphingosine 1-phosphate receptors on lymphocytes, inhibiting egress of lymphocytes from the lymph nodes and thereby preventing entry of lymphocytes into the blood and their subsequent infiltration into the CNS.<sup>26</sup> A 2010 study published by Cohen et al<sup>27</sup> demonstrated the superior efficacy of oral fingolimod with respect to relapse rates and MR imaging outcomes in patients with MS, compared with intramuscular IFN $\beta$ . In 2012, 2 different neurologic complications of fingolimod treatment came to light. Visser et al<sup>28</sup> reported that MS plaques paradoxically worsened after fingolimod treatment in 3 patients who started fingolimod 3–4 months after stopping another second-line therapy, natalizumab (NTZ). Furthermore, a woman who developed tumefactive MS lesions 6 months after starting fingolimod, without previously receiving NTZ, was described.<sup>28</sup>

A second complication was the development of herpes zoster encephalitis after commencement of fingolimod. Cohen et al<sup>29</sup> described 2 fatal cases of herpes encephalitis in 2 patients on fingolimod therapy. Recent studies have shown that the overall rates of varicella zoster infections in clinical trials were low with fingolimod but higher than in placebo recipients (11 versus 6 per 1000 patient-years).<sup>30</sup>

**Natalizumab.** The migration of lymphocytes across the blood-brain barrier is an important step in the creation of inflammatory lesions in MS, with the presence of leukocytes within the cerebral perivascular spaces deemed a pathologic hallmark.<sup>31</sup> Natalizumab (NTZ, Tysabri) is a monoclonal antibody administered intravenously that binds to proteins on the surface of lymphocytes and inhibits binding of the cell to the luminal surface of blood vessel walls.<sup>32</sup> On MR imaging, NTZ has demonstrated a reduction in the development of new gadolinium-enhancing lesions,<sup>33</sup> and a significant reduction in the conversion of gadolinium-enhancing lesions to T1-hypointense lesions.<sup>34,35</sup> This reduction in lesion formation was greater than the previous reduction of 50%–80% and 30% reported with IFN $\beta$  and glati-

ramer acetate, respectively.<sup>14,36</sup> Even within 2 months of treatment, NTZ has been associated with a >90% reduction in new MR imaging gadolinium-enhancing lesions compared with a placebo.<sup>32</sup> Clinically, patients treated with NTZ have significantly fewer clinical relapses, and it is currently the only disease-modifying therapy to actually improve the Expanded Disability Status Scale in select patients.<sup>37</sup>

In 2005, NTZ was withdrawn from the market as a result of the potentially lethal adverse effect of PML occurring in 3 separately reported patients.<sup>38–40</sup> PML results from an opportunistic infection of the oligodendrocytes caused by the reactivation and replication of the John Cunningham polyomavirus.<sup>41</sup> As of March 4, 2016, 635 cases of PML in patients treated with NTZ have been reported.<sup>42</sup> Despite a widespread understanding of the major risk factors for PML, the overall rate of NTZ-associated PML has nearly doubled between 2012 and 2015.<sup>43</sup> The imaging features of PML are discussed in the Part 2 of this review.

**Alemtuzumab.** Alemtuzumab (Lemtrada) is a monoclonal antibody that effects circulating T- and B-lymphocytes, leading to alterations in the number and functions of lymphocyte subsets.<sup>44</sup> Alemtuzumab received FDA approval in the treatment of RRMS in November 2014. It is administered intravenously during 2 treatment courses for a total of 8 days and is associated with infusion reactions in essentially all treated patients. In its Phase III trials, alemtuzumab, compared with IFN $\beta$  given subcutaneously, reduced the annualized relapse rate by 49%–55%, the rate of disability progression by 30%–42%, and the number of gadolinium-enhancing lesions by 61%–63%.<sup>44,45</sup> Tuohy et al<sup>46</sup> reported secondary autoimmunity as the most frequently reported adverse event posttreatment. Such conditions included thyroid disorders (41% of 86 patients treated) most commonly, followed by immune thrombocytopenic purpura (3.5%) and, rarely, nephropathies, namely Goodpasture syndrome (<1%).<sup>46</sup> Thyroid disorders included hyperthyroidism, hypothyroidism, thyroiditis, and rarely goiter formation. Most cases occurred within 2 years of the last infusion.<sup>45</sup> On the basis of the risk of autoimmune-mediated conditions, monthly blood and urine analyses are recommended for 4 years after the last dose of alemtuzumab.<sup>5</sup>

**Mitoxantrone.** Mitoxantrone is an anthracenedione chemotherapeutic agent that inhibits T-cell activation and reduces proliferation of B- and T-cells.<sup>19</sup> Limited efficacy data are available, but controlled studies of patients with highly active RRMS have shown significant efficacy of the treatment, as shown by a 60%–70% reduction in the relapse rate (compared with placebo or IV steroids) and reduced disability progression and MR imaging evidence of disease activity.<sup>5,47,48</sup> Mitoxantrone is currently the only agent approved to treat secondary-progressive multiple sclerosis.<sup>49</sup> Adverse events such as transient nausea, fatigue, mild hair loss (for days to a week), and menstrual disturbances are frequent (60%–70%).<sup>49</sup> Additional adverse events are urinary tract infection (about 30%) and elevated liver enzymes and leukopenia (about 15%–20%). Although not in the Phase III trial, lethal congestive heart failure and therapy-related leukemia have been reported in treated patients, even years after treatment ends.<sup>50,51</sup> Due to this potential cardiotoxicity, echocardiograms should be performed before, during, and after treatment. Mitoxantrone is

teratogenic and is absolutely contraindicated in pregnancy. The use of mitoxantrone has rapidly decreased due to the risk of severe complications and the increasing number of alternative highly effective and less toxic treatment options.<sup>5</sup>

### **Future Therapeutic Directions**

**Monoclonal Antibodies.** Several other monoclonal antibodies against various lymphocyte surface markers are currently being investigated in the treatment of MS.<sup>4</sup> Daclizumab, an antibody against CD25<sup>+</sup> T-cells, is presently in late-stage clinical trials.<sup>52</sup> Ocrelizumab<sup>53</sup> and ofatumumab,<sup>54</sup> monoclonal antibodies directed against the CD20 surface marker on B-cells, have been designed to minimize infusion-related reactions and are currently under investigation for various forms of MS. Rituximab, a human-mouse chimeric monoclonal antibody against CD20, has also been used off-label for a small group of patients who did not respond to the approved second-line treatments.<sup>55</sup>

**Autologous Hematopoietic Stem Cell Transplantation.** There are published reports of >600 bone marrow–based transplants performed primarily for the treatment of MS.<sup>56</sup> Hematopoietic stem cell transplantation appears to be most beneficial for patients with highly active MS who are progressing and who are refractory to conventional MS therapies.<sup>56,57</sup> It is too early, however, to recommend a more widespread use of hematopoietic stem cell transplantation until more data from randomized controlled trials are available. Currently, there is at least 1 Phase III trial addressing this issue.<sup>57</sup>

### **Role of the Radiologist in MS Surveillance and Pharmacovigilance**

**Standardized Imaging.** MR imaging is the most sensitive tool currently available for monitoring inflammatory disease activity in MS. Clinical assessments far underestimate disease activity and burden compared with MR imaging.<sup>58</sup> The challenge with using MR imaging as a surrogate for clinical outcomes is the lack of standardization and the variability in the interpretation of findings.<sup>58</sup>

The use of MR imaging in the routine follow-up of patients with MS is less straightforward than its use in the diagnostic process, owing largely to the experimental nature of many of the techniques that have been used to measure disease progression.<sup>59</sup> Although follow-up MR imaging studies should be as consistent as possible with baseline or reference scans, fewer sequences are necessary than have been recommended for the initial diagnosis of MS and can be completed in 20–25 minutes.<sup>59,60</sup> Often follow-up imaging can be tailored on the basis of the specific indication. For example, to assess treatment efficacy, FLAIR and T2-weighted spin-echo sequences should be used, whereas DWI, and SWI if available, should also be included for patients at risk of PML.<sup>58,59,61,62</sup>

Gadolinium has routinely been administered in many centers as part of their MS follow-up imaging protocol. Gadolinium-enhancing lesions are considered a marker of blood-brain barrier disruption, which has been associated with acute inflammation in patients with MS.<sup>58,63</sup> Contrast-enhancing lesions are also typically easier to identify than new and/or enlarged T2 hyperintense

## Summary of imaging parameters

Segment	Sequences	Plane	FOV (mm)	Matrix	Thickness (mm)	TR (ms)	TE (ms)	TI (ms)	No. of Signals Acquired
Brain	T2	Axial	220	512 × 384	4	6000.0	100.0	—	1
Brain	FLAIR	Axial	220	320 × 224	4	7500.0	81.0	2500 ms	1
Brain	FLAIR	Sagittal	220	320 × 224	4	7500.0	81.0	2500 ms	1
Brain	T1	Sagittal	230	224 × 224	0.9	2300.0	2.3	—	1
Cervical	T2	Axial	180	256 × 218	3	555.0	17.0	—	2
Cervical	T2	Sagittal	240	384 × 269	3	3000.0	102.0	—	1
Cervical	T1	Sagittal	240	384 × 269	3	600.0	9.5	—	2

lesions, and the process is also less dependent on technical factors such as scan repositioning. Furthermore, some new T2 hyperintense lesions are only detected after being identified as new enhancing lesions, owing to their small size or location in areas with confluent lesions.<sup>64</sup> Interobserver accuracy is also significantly better when looking for gadolinium-enhancing lesions rather than new T2-lesions. A 2013 study by Erbayat Altay et al<sup>65</sup> found that concordance correlation was high (0.8–0.96) for gadolinium-positive lesions, intermediate (0.6–0.8) for new T2 lesions, and very poor (0.0–0.14) for T2 enlarging lesions.

On the other hand, recognition of disease activity cannot rely exclusively on enhancing lesions. New inflammatory lesions take up gadolinium for approximately 3–4 weeks after their development, and the recommended interval between baseline and follow-up scans is typically 6 months.<sup>66</sup> Therefore, although enhancing lesions are useful, they are not sufficiently sensitive to act as sole measures of disease activity.<sup>59</sup> Recent studies have suggested that gadolinium-based contrast agents can accumulate in the brains of patients who have undergone multiple contrast-enhanced MR imaging studies.<sup>67</sup> The most recent guidelines recommend that clinicians carefully evaluate the necessity of gadolinium use and limit it only to those cases in which the additional information provided is clinically significant.<sup>68,69</sup> In light of these studies and the transient nature of enhancing lesions, contrast administration for patients undergoing surveillance MR imaging is not routinely performed at our institution unless there is an unexpected change of clinical status or a high clinical suspicion for relapse of disease.

Standardized patient head positioning and image acquisition, ideally with the same field strength, and access to prior MR imaging are critical for the accurate assessment of changes in lesion size and number with time.<sup>62</sup> All scans should be obtained at field strengths of at least 1.5T. Higher field strengths, for example 3T, have the advantage of detecting a higher lesion load compared with 1.5T imaging.<sup>70</sup> Imaging findings should not be taken out of clinical context. A study performed by Neema et al<sup>71</sup> demonstrated that in healthy subjects, the total number and volume of discrete FLAIR hyperintense foci of age-related and incidental hyperintensities were nearly double on 3T versus 1.5T. In our practice, when comparing 3T imaging with prior 1.5T imaging, we are careful to only declare lesions as new if they are of a size and signal intensity that would have been visible if present on prior 1.5T imaging.

In our institution, MR imaging in suspected or known MS is performed using a 3T MR imaging system (Magnetom Skyra; Siemens, Erlangen, Germany) with acquisition parameters outlined in the Table. We use a guideline-based<sup>58,60,62,72</sup> standardized diagnostic MS brain MR imaging protocol. For brain imaging, we

always include axial 2D T2 TSE, 2D axial and sagittal FLAIR, and 3D pre- and post-contrast-enhanced T1 sequences. Additional sequences may include axial diffusion-weighted imaging and SWI, depending on clinical circumstances. For brain MR imaging surveillance, we do not routinely acquire contrast-enhanced T1 imaging. Our standardized diagnostic and surveillance cervical spinal cord MR imaging protocol always includes sagittal T2 TSE and axial T2 gradient-echo sequences. Optional sequences in the cervical spine include an additional T2-weighted sagittal sequence (eg, STIR and pre- and postcontrast T1 imaging in the sagittal and axial planes). Gadolinium is administered (single dose, 0.1 mmol/kg body weight) with a minimum 5-minute delay before postgadolinium T1 sequence acquisition.<sup>73</sup> A further dose of gadolinium is not administered for MR imaging of the cervical spine, provided it immediately follows the contrast-enhanced brain MR imaging study.

While MR imaging is a powerful noninvasive tool routinely used in the diagnosis and monitoring of MS, certain limitations of conventional MR images exist. FLAIR is one of the most sensitive techniques for visualization of supratentorial white matter lesions<sup>74,75</sup>; however, it is less sensitive than 2D T2 TSE in detecting posterior fossa lesions.<sup>75,76</sup> This difference can be compensated for by using FLAIR at a higher strength magnetic field (3T) and/or with a 3D T2 FLAIR sequence, but T2 TSE remains slightly more sensitive in the detection of infratentorial lesions.<sup>77–79</sup> MS protocols should thus include a T2 TSE sequence, which should be specifically examined when assessing the infratentorial brain.

A second pitfall of routine brain MR imaging sequences is the difficulty in detection of gray matter MS lesions.<sup>80</sup> White matter lesions are readily detected on standard MR imaging protocols; however, most cortical gray matter plaques are not. Cortical gray matter lesions are common in MS<sup>81</sup> and are associated with physical disability and cognitive impairment.<sup>82,83</sup> The difficulty in the detection of cortical gray matter lesions is mainly due to their small size<sup>84</sup> but also due to the lower degree of inflammation associated with cortical lesions, the lower amount of myelin in the cortex compared with white matter, and partial volume artifacts from the adjacent CSF and white matter.<sup>85</sup> Although not routinely available, ultra-high-field MR imaging (for example, 7T) has significantly improved the detection of gray matter cortical lesions.<sup>86</sup> Furthermore, advances in pulse sequences, including double inversion recovery<sup>87,88</sup> or phase-sensitive inversion recovery,<sup>89</sup> are recently developed techniques to overcome this obstacle, which may become more widespread in time.

Third, MR spinal cord imaging is more challenging than brain MR imaging<sup>90</sup> because the spinal cord is long, thin, and mobile. Imaging is made more difficult by ghosting (from



breathing and pulsation of CSF and blood) and truncation artifacts.<sup>91</sup> Poor histopathologic correlation between T2 imaging and MS-associated pathologic spinal cord change is well-described.<sup>92,93</sup> Some authors recommend 2 sets of sagittal images to improve confidence in lesion detection.<sup>90,94</sup> Sagittal sequences could include T2, proton density, STIR, or T1-weighted inversion recovery with phase-sensitive inversion recovery. In our experience, axial imaging is a much more reliable and sensitive technique in the detection of small plaques that often have a more lateral location in the cord (where volume-averaging artifacts are more common on sagittal sequences). We routinely acquire axial imaging through the entire cervical cord (rather than acquire a second sagittal sequence) and more targeted axial imaging in the thoracic cord and conus if potential lesions are seen on sagittal imaging.

### **Imaging the Brain versus the Spinal Cord**

Focal abnormalities in the spinal cord are present in most patients with MS, affecting the cervical region more frequently than the thoracic and lumbar regions.<sup>95</sup> MR imaging of the spinal cord is more challenging than brain MR imaging for reasons outlined above. These inherent features make it difficult to image subtle pathologic changes and to ensure comparability in follow-up examinations. Sagittal T2-weighted MR imaging can demonstrate larger lesions and should always be examined, but axial T2-weighted imaging is the most accurate and useful in detecting the commonly small peripheral lesions.<sup>96</sup>

Although newer imaging modalities have improved the detection of spinal cord lesions in MS,<sup>95</sup> conventional MR imaging still lacks the necessary histopathologic specificity.<sup>97</sup> Recent research has been focused on quantitative techniques such as the measurement of spinal cord atrophy. Spinal cord atrophy correlates with clinical disability,<sup>98-100</sup> and its association with disability is stronger than with focal lesion load.<sup>101</sup> Quantification of spinal cord volume or cross-sectional area with MR imaging may be a potential marker for monitoring the disease course or treatment effectiveness in the future.

Brain imaging is still considered a more sensitive surveillance tool than spinal cord imaging for longitudinal monitoring of patients with MS.<sup>59</sup> Brain imaging is more likely to identify subclinical inflammation, whereas inflammation affecting the spinal cord is more likely to be symptomatic.<sup>102</sup> Several studies have shown that MR imaging of the spinal cord is less sensitive than brain MR imaging for detecting disease activity, particularly with regard to contrast-enhancing lesions, relating mostly to image artifacts associated with vascular and CSF pulsation. Routine spinal imaging is therefore not currently recommended as part of MR imaging surveillance schedules.<sup>103,104</sup> MR imaging of the spinal cord may be indicated when there is significant clinical worsening with few changes on brain MR imaging or to rule out an alternative cause of progressive myelopathy, such as cervical spondylosis or a tumor. Routine follow-up with spinal cord imaging may be useful in patients with known spinal cord disease, in rare cases of recurrent transverse myelitis to assess response to therapy, or in new disease activity.<sup>58</sup>

### **Pharmacovigilance on Disease-Modifying Therapy and Frequency of Surveillance**

Several guidelines have attempted to define the indications for and frequency of serial MR imaging in patients with an established diagnosis of MS.<sup>62,105,106</sup>

Follow-up MR imaging should be performed on at least an annual basis in patients with MS, especially for the first 2 or 3 years after starting therapy. However, certain patients at risk of serious treatment-related adverse events may need to be monitored more frequently, for example, every 3–4 months.<sup>59</sup> A 2015 publication by the Magnetic Resonance Imaging in MS Consortium recommends that patients be evaluated with MR imaging after each unexpected clinical presentation whether typical or atypical of MS.<sup>59</sup>

Since the approval of the most recent generation of MS therapeutics, the importance of the role of MR imaging in MS drug surveillance is increasing. The aims of MR imaging drug surveillance include detection of unexpected MS disease activity, paradoxical reactions (eg, tumefactive demyelinating lesions), comorbidities (eg, vascular, neoplastic), and adverse effects such as PML and other opportunistic infections.<sup>107,108</sup> The importance of strict pharmacovigilance has been recognized for many years, but it has gained additional clinical relevance with the potential for a broader spectrum of adverse findings than with earlier therapies.<sup>109</sup>

Part 2 of this review will discuss the recommended frequency of MR imaging for patients, depending on their treatment regimen and their unique risk profile. Further, it will focus on the imaging features that are important for neuroradiologists to be aware of when interpreting images in patients being treated with the most recent MS medications. The second part of this review will also examine the various methods for assessing the radiologic response to MS therapies. Finally, it covers future areas and technologies that may make the accomplishment of the above tasks more reliable and efficient.

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