Consensus opinion of US neurologists on practice patterns in RIS, CIS, and RRMS

Evolution of treatment practices

Carlo Tornatore, MD; J. Theodore Phillips, MD, PhD; Omar Khan, MD; Aaron E. Miller, MD; Mark Hughes, PhD

Abstract

Purpose of review: To assess current practice patterns of US neurologists in patients with radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS), and relapsing-remitting multiple sclerosis (RRMS) using case-based Web surveys.

Recent findings: We identified a total of 47 points of consensus ($\geq 75\%$ agreement) with regard to diagnosis, treatment, and monitoring of RIS, CIS, and RRMS. Current US treatment consensus patterns emphasize (1) MRI in multiple sclerosis (MS) diagnosis and subsequent treatment decisions, (2) treatment of early disease, (3) aggressive initial treatment of highly active MS, and (4) close patient monitoring for clinical response and adverse effects of disease-modifying drugs. **Summary:** These findings may offer insights into harmonizing MS care and represent the first steps in potentially establishing a more uniform approach to the treatment of patients with MS in the United States without compromising the need for individual treatment for each patient. *Neurol Clin Pract* 2016;6:329-338

Appropriate choice of medication for the treatment of multiple sclerosis (MS) is becoming increasingly complex as new therapies are approved¹; it is unlikely that sufficient Class I evidence will be obtained to establish a robust treatment algorithm. This study aimed to generate consensus opinions on MS management and treatment practices based on current clinical practices of US MS experts.

The study also investigated the evolution of treatment practices by comparing current responses with those from a related 2011 consensus survey conducted in 75 US neurologists² in a subset of 50 respondents who participated in both surveys. At the time the survey was undertaken, the following therapies were approved for use in MS by the US Food and Drug

Medstar Georgetown University Hospital (CT), Washington, DC; Baylor Institute for Immunology Research (JTP), Dallas, TX; Wayne State University School of Medicine (OK), Detroit, MI; Icahn School of Medicine at Mount Sinai (AEM), New York, NY; and Infusion Communications (MH), Haddam, CT.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Correspondence to: tornatoc@gunet.georgetown.edu

Editorial, page 288

Assessment of changes in treatment practices were made by comparing results with related surveys conducted in 2011, which used analogous patient scenarios.

Administration (FDA): the injectable therapies interferon- β (IFN- β)–1a (both intramuscular and subcutaneous [SC] formulations), IFN- β -1b (SC formulation), and glatiramer acetate (GA); the oral medications fingolimod, dimethyl fumarate, and teriflunomide; and the infusion treatments natalizumab and mitoxantrone.

METHODS

A total of 239 MS experts identified from the Consortium of Multiple Sclerosis Centers (CMSC) list of treatment centers were invited to participate in the study. Final participants were self-selected based on a willingness to complete 2 serial, Web-based surveys developed and distributed by a steering committee of 6 MS experts independent of the CMSC and 2 representatives from large national health plan and pharmacy benefits managers. A modified Delphi process^{3,4} was employed to assess current MS practice patterns by evaluating the use of various diagnostic and clinical parameters in decisions pertaining to diagnosis and to selection, initiation, maintenance, and switching of disease-modifying therapies (DMTs). Hypothetical patient scenarios were presented detailing key clinical/MRI findings in cases involving clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), or relapsing-remitting MS (RRMS).

Both surveys used identical scenarios; the second survey allowed clarification and expansion of responses from the first survey. Respondents were asked to base therapy decisions on clinical evidence alone and assume no payer restrictions. Although all available MS therapies were included in the survey and respondents were free to choose between, for example, different formulations of IFN- β , the steering committee agreed that the overall efficacy of injectable therapies was similar. Hence, to simplify the assessments, the results for injectable therapies were combined. Results for oral therapies were also combined to enable comparisons with the 2011 survey, as at that time there was only 1 oral treatment with approval from the FDA. This combination was not based on any assumptions about the comparative efficacy or tolerability of these therapies.

The respondents were also asked questions relating to other clinical practices related to the care of patients with MS, which included MRI assessments, discussion with patients on treatment options and changes, smoking, vitamin D, and treatment practices during pregnancy and breast-feeding.

The surveys, accessed via a secure e-mail link, were administered between December 2013 and April 2014 and included all DMTs approved by the FDA for the treatment of MS as of December 2013.

Respondents were made aware in the first survey that the study was supported by an educational grant from Biogen, that the steering committee had made every effort to avoid bias, and that the surveys were free of commercial influence. All survey respondents remained anonymous to the study steering committee. Consensus opinion was defined a priori as $\geq 75\%$ agreement, with unanimous (100%) and majority ($>50\%$) opinions also reported; opinion percentages are accompanied by 95% confidence intervals. Statistical differences in proportions were estimated using Fisher exact test.

Assessment of changes in treatment practices were made by comparing results with related surveys conducted in 2011,² which used analogous patient scenarios. Detailed study methods are provided in appendix e-1 at Neurology.org/cp.

RESULTS

Respondents ($n = 107$) came from both academic (49%) and community (51%) MS treatment centers, had been treating patients with MS for an average of 21 years, and represented a diverse

Supplemental Data

Neurology.org/cp

Table 1 Consensus points

Form of MS	Consensus points (≥75% of respondents)
RIS	Initiation of treatment would not be appropriate (79%)
	Of the participants who would not initiate treatment, 100% would obtain a follow-up brain MRI, with 82% doing so within 12 months
	A spinal cord MRI would be performed as part of the diagnostic evaluation (94%)
	Presence of >2 Gd+ lesions would prompt treatment initiation (80%)
CIS	As part of the diagnostic evaluation, a brain MRI (100%) and spinal cord MRI (76%) would be performed
	Optic neuritis without MRI activity is an insufficient basis for DMT initiation (96%)
	Performing a follow-up MRI in untreated patients is appropriate (99%) and would be done within 12 months of presentation (75%)
	Treatment initiation would be appropriate for a patient with optic neuritis with ≥2 nonenhancing brain T2 lesions (93%) or ≥1Gd+ lesion in addition to nonenhancing lesions (100%)
	Lumbar punctures would not be performed in a patient with Gd+ lesions (85%)
RRMS	Lumbar punctures would also not be performed in a patient presenting with optic neuritis alone (67%) or optic neuritis and nonenhancing T2 lesions (63%)
	Start treatment-naïve patients with RRMS and recent clinical and MRI activity on a DMT (100%)
	Although initial therapy in patients with mild symptoms is open to physician preference, patients with active disease would be treated with natalizumab if they are JCV– (89%)
	Consensus was achieved that patients who are JCV+ would be transitioned to an oral therapy if they have had suboptimal responses to their existing therapy irrespective of whether they were receiving an injectable therapy (84%), a different oral therapy (76%), or natalizumab (90%); JCV– patients with a suboptimal response to natalizumab would be transitioned to an oral therapy (83%)
	Performing a follow-up MRI within 6 months of treatment initiation is appropriate (75%)
General	Treatment continuation is appropriate even if a patient remains clinically and MRI stable for 5 years (86%)
	All available and approved therapies would be discussed with newly diagnosed patients (88%)
	Asymptomatic MRI activity was considered the biologic equivalent of a clinical relapse and generally requires treatment (81%)
	Vitamin D levels would be checked (97%), actively monitored (86%), and supplemented if low (99%) to achieve a target level in the mid-to-high normal range (88%)
	DMTs would be discontinued in patients who become pregnant (79%)
	Use of a DMT while breast-feeding was not supported (75%)
Abbreviations: CIS = clinically isolated syndrome; DMT = disease-modifying therapy; Gd+ = gadolinium-enhancing; JCV = JC virus; MS = multiple sclerosis; RIS = radiologically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis.	

range of US geographic regions (figure e-1). Overall, 90% (83.5%–95.3%) of the respondents concurred that the survey did not appear to have been influenced by the study sponsor. Retention of respondents was high, with 103 of the 107 respondents (96%) completing both surveys. Fifty of the physicians completed both the current and 2011 surveys.

Table 1 provides an overall summary of consensus points; figure 1 offers a summary of treatment practices.

Practice patterns for RIS

Case A 31-year-old woman underwent a brain MRI for evaluation of migraines that revealed incidental white matter findings (3 nonenhancing periventricular T2 lesions, 1 juxtacortical lesion, and 1 cerebellar lesion) highly suggestive of inflammatory demyelination. Neurologic examination results were normal. Medical history and family medical history were unremarkable. (The 2011 survey specified that the patient had 4 nonenhancing periventricular T2 lesions.)

Figure 1 Treatment practices

CIS = clinically isolated syndrome; DMT = disease-modifying therapy; Gd+ = gadolinium-enhancing; JCV- = JC virus; RIS = radiologically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis.

A majority of respondents (67% [58.4%–76.2%]) would perform a lumbar puncture (LP), a large increase from the 2011 survey (37% [26.4%–48.2%]).

There was consensus in favor of performing a spinal MRI (94% [88.8%–98.2%], increased from 88% [80.7%–95.3%]) but not for initiating treatment if the MRI results were normal (21% [13.0%–28.2%], increased from 11% [3.7%–17.6%]). A majority, but not a consensus (72% [63.1%–80.5%], decreased from 86% [78.4%–94.2%]), favored not beginning treatment if the brain MRI showed only nonenhancing activity.

There was consensus (80% [71.9%–87.7%]) to initiate treatment if >2 gadolinium-enhancing (Gd+) lesions were observed and majority agreement (70% [61.1%–79.0%]) if 1 or 2 Gd+ lesions were observed.

There was unanimous agreement (increased from 88% [80.7%–95.3%] in 2011) about performing a follow-up MRI and consensus (82% [74.0%–91.0%]) about undertaking it within 12 months.

Practice patterns for CIS

Case. A previously healthy 24-year-old woman presented with visual acuity loss in her right eye. Optic neuritis was confirmed, and neurologic examination results were normal.

As in 2011, there was unanimous agreement on the need to perform a brain MRI.

There was consensus (96% [92.7%–99.9%], decreased from 99% [96.1%–100%] in 2011) that if no MRI activity was observed, optic neuritis alone was insufficient evidence for treatment initiation.

A majority (67% [58.4%–78.2%], decreased from 80% [71.0%–89.0%] in 2011) believed that an LP was unnecessary.

There was consensus (76% [67.3%–83.7%], increased from 69% [58.9%–79.7%] in 2011) on the need to obtain a spinal cord MRI.

There was consensus (99% [97.1%–100%], up from 93% [87.5%–99.0%] in 2011) for obtaining a follow-up MRI within 12 months of clinical presentation (75% [66.7%–83.3%]).

Treatment decisions based on modifications of this case were also investigated.

Initial presentation revealed ≥2 nonenhancing T2 lesions There was consensus (93% [88.4%–98.1%]) for treatment initiation, with a majority (58% [47.9%–67.3%]) prescribing IFN-β or GA, 32% (23.1%–41.5%), preferring an oral medication, and 9% (3.5%–14.8%) choosing natalizumab as the most appropriate therapy.

A majority (63% [55.1%–73.7%], decreased from 69% [58.9%–79.7%] in 2011) would not perform an LP.

Initial presentation revealed 1 Gd+ corpus callosum lesion, 3 nonenhancing periventricular lesions, and 1 nonenhancing cerebellar lesion Agreement on initiating therapy was unanimous but no agreement on choice of therapy. In patients negative for anti-JC virus (JCV) antibodies, 38% (29.4%–48.2%) of respondents would initiate treatment with IFN- β or GA, 35% (25.8%–44.2%) with an oral medication, and 25% (16.8%–33.6%) with natalizumab. In anti-JCV-antibody positive patients, 56% (46.8%–65.9%) of respondents would initiate treatment with an oral medication, 38% (29.4%–48.2%) with IFN- β or GA, and 4% (0.2%–7.6%) with natalizumab.

There was consensus (85% [78.6%–92.2%], similar to the 84% [75.7%–92.3%] reported in 2011) that there was no need to perform an LP.

Practice patterns for RRMS

Case. A 25-year-old treatment-naïve man with RRMS presented with (1) 2 clinical relapses in the last 4 years (1 within the last 6 months), a normal neurologic examination, and 5 nonenhancing T2 lesions on brain MRI, or (2) 2 clinical relapses in the last 4 years (1 within the last 6 months) with residual disability; multiple nonenhancing brain, brainstem, and spinal cord lesions; hypointense T1 lesions (black holes); and brain atrophy. (In the 2011 survey, no time scale was given for the latest relapse, and there was no scenario 2.)

There was unanimous agreement in both cases on initiating DMT.

In both cases, there was consensus that a follow-up MRI would be performed within 12 months (97% [93.9%–100%]) or 6 months (75% [66.3%–83.3%]).

Patient scenario 1 There was no consensus on choice of therapy. A total of 42% (32.8%–51.4%) would prescribe an oral treatment. A total of 38% (29.1%–47.5%) (decreased from 100% in 2011) would prescribe an injectable therapy. A total of 13% (6.7%–19.4%) would prescribe natalizumab. A total of 7% (1.8%–11.2%) did not specify any particular therapy type.

There was consensus (86% [79.5%–92.6%]) in favor of continuing treatment with a DMT even if the patient had remained clinically and MRI stable for 5 years.

Patient scenario 2 The choice of therapy was dependent on the patient's JCV status. The only consensus (89% [83.2%–95.2%]) was for prescribing natalizumab to JCV– patients (figure 2).

Changing therapies

No consensus was achieved on the amount of new MRI activity that would prompt a change in DMT; the majority of respondents agreed that a change would be considered if, after 2 years, at least 2 new T2 lesions (66% [56.5%–74.9%]) or 1 new Gd+ lesion (52% [42.3%–61.7%]) were observed in an asymptomatic patient with RRMS. When the period of stability was increased to 3 years, a change in therapy would be considered if new T2 or Gd+ lesions were reported by 69% (59.6%–77.6%) or 47% (37.4%–56.8%) of respondents, respectively.

Table 2 shows the preferred choice of alternative therapy for a patient with a suboptimal response to current therapy, based on each respondent's own personal criteria. There was consensus (>90%) in favor of transitioning patients with a suboptimal response while on an injectable therapy to a noninjectable therapy. There was consensus in favor of maintaining treatment with an oral therapy (76%) or transitioning JCV+ patients from an injectable (84%) or IV (90%) treatment to an oral therapy. There was consensus (83%) in favor of switching JCV– patients with a suboptimal response while on natalizumab to an oral treatment. A majority (69%) would transition JCV– patients with a suboptimal response while on an oral therapy to natalizumab; only 21% would transition JCV+ patients from an oral therapy to natalizumab.

Participants were also asked about washout periods when transitioning patients between therapies. There was consensus that no washout was required when transitioning from GA

Figure 2 Choice of initial treatment in patient with relapsing-remitting multiple sclerosis with 2 clinical relapses in the last 4 years (1 within the last 6 months), brain hypointense T1 lesions, and brain atrophy (n = 101)

IFN = interferon; JCV = JC virus; SC = subcutaneous.

(91% [84.9%–96.1%]) or IFN- β (80% [72.4%–87.6%]). A majority (65% [56.3%–74.5%]) would not include a washout period when switching from dimethyl fumarate. There was no consensus or majority agreement for other DMTs; suggested washout periods ranged from 0 to 3 months for fingolimod and from 0 to ≥ 6 months for natalizumab and teriflunomide.

Subanalysis of individual changes in clinical practice between 2011 and 2014

Fifty respondents completed both the 2011 and 2014 surveys, allowing an assessment of individual changes in treatment practices over this period. It is to be expected that the responses and changes in responses from these 50 physicians will not directly mirror those observed from the

Table 2 Therapeutic choice following suboptimal response to original therapy by anti-JCV antibody status (n = 99–101)

	New therapy					
	JCV–			JCV+		
Original therapy	Injectable ^a	Oral ^b	IV	Injectable ^a	Oral ^b	IV
Injectable ^a	9.2 (3.6–14.8)	44.9 (35.2–54.6)	46.0 (36.3–55.7)	9.5 (3.8–15.2)	83.8 ^c (76.6–91.0)	6.7 (1.8–11.6)
Oral ^b	3.0 (0–6.3)	27.8 (19.1–36.5)	69.2 (60.2–78.2)	3.7 (0–7.4)	75.7 (67.4–84.0)	20.6 (12.7–28.5)
IV	2.0 (0–4.7)	83.2 ^c (75.9–90.5)	14.9 (8.0–21.8)	2.0 (0–4.7)	89.9 ^c (84.4–95.8)	8.1 (2.8–18.4)

Abbreviation: JCV = JC virus.

^aGlatiramer acetate or interferon- β .

^bDimethyl fumarate, fingolimod, or teriflunomide.

^cConsensus.

Values are percentage (95% confidence limits) of respondents.

entire survey; however, only major discrepancies (>10% difference) between the 2 populations are noted.

RIS case scenario Both surveys showed that 90% (81.7%–98.3%) of the physicians would carry out a spinal cord MRI and that all 50 respondents would schedule a follow-up brain MRI.

There was a small decrease in the percentage of physicians who would not order an LP (64% [50.7%–77.3%] in 2011 vs 60% [46.4%–73.6%] in 2014). This is in contrast to the whole population, where there was a small increase (63% vs 67% [58.4%–76.2%]).

A greater percentage of physicians would now initiate treatment with a DMT (10% [1.7%–18.3%] vs 26% [13.9%–38.1%]; $p = 0.0664$).

Patient with CIS with no evidence of MRI activity There were increases in the percentage of physicians who would do the following: carry out a follow-up brain MRI (92% [84.5%–99.5%] in 2011 vs 100% in 2014); carry out a spinal cord MRI (62% [48.6%–75.4%] vs 76% [64.2%–87.8%]); initiate DMT (2% [0%–5.9%] vs 4% [0%–9.4%]); and request an LP (28% [15.6%–40.4%] vs 30% [17.3%–42.7%]). For the overall population, there was a greater increase in the percentage of physicians who would request an LP for this patient (20% vs 33% [23.8%–41.6%]).

Patient with CIS with MRI activity More physicians would now carry out a spinal cord MRI (74% [61.9%–86.1%] in 2011 vs 88% [79.0%–97.0%] in 2014). There was no change in the small percentage of physicians (15% [5.9%–26.2%]) who would request an LP. The percentage who would initiate treatment remained similar (98% [94.1%–100%] vs 100%). In 2011, all physicians initiating therapy would prescribe IFN- β or GA; only 52% (38.2%–65.8%) would now continue to initiate DMT with these treatments ($p < 0.0001$). Of the rest, 30% (17.3%–42.7%) would prescribe an oral therapy, 14% (4.4%–23.6%) would initiate natalizumab, and 4% (0%–9.4%) did not specify any particular treatment.

Individual changes for each of these 3 patient scenarios are summarized in table e-1.

Patient with RRMS There was a >3-fold reduction in the percentage of physicians who would initiate treatment with IFN- β or GA (57% [43.3%–70.7%] in 2011 vs 18% [7.4%–28.6%] in 2014; $p = 0.0001$).

More physicians would now initiate treatment with natalizumab (39% [25.5%–52.5%] vs 63% [49.6%–76.4%]; $p = 0.0257$). This increase was not seen in the overall population (32% [19.1%–44.1%] vs 37% [23.6%–50.4%]; $p = 0.5930$).

A greater percentage of physicians would now initiate treatment with fingolimod (4% [0%–9.4%] vs 16% [5.9%–26.2%]), the only oral therapy available at the time of the 2011 survey.

A majority of physicians (56% [42.3%–69.7%]) would now initiate treatment with a different DMT from their preferred treatment choice in 2011.

Other consensus points observed from the complete 2014 survey group

In addition to the patient case scenarios, the current surveys also elicited responses regarding other clinical practices related to the care of patients with MS. These findings are summarized as follows (with percentage agreement in parentheses).

New, asymptomatic MRI activity was considered the biologic equivalent of a clinical relapse (81% [73.3%–88.4%]). MRI scans are personally reviewed as part of the routine care of patients (98% [95.5%–100%]). All available and approved treatment options would be discussed with newly diagnosed patients (88% [82.2%–94.6%]); 76% (67.0%–84.6%) of these respondents would recommend a specific treatment following discussion.

Over the previous 12 months, 75% (66.8%–83.6%) of respondents had prescribed treatment for all their patients with relapses; all respondents had treated some patients with acute relapses with IV corticosteroids. Physicians would consider changing prescribed therapy if they suspected patient nonadherence (99% [97.1%–100%]) or if the patient expressed concerns over the safety (94% [89.7%–98.7%]) or tolerability (97% [93.9%–100%]) of current therapy.

[T]he emergence of oral therapies has had a noteworthy effect on prescribing practices, particularly as alternatives for patients with a suboptimal response to other treatments.

Patients were counseled against smoking (95% [91.0%–99.2%]). Vitamin D levels were checked (97% [93.9%–100%]) and actively monitored (86% [79.8%–93.0%]); deficient patients would be prescribed a supplement (99% [97.1%–100%]). Target levels of vitamin D were not clear, but there was consensus (88%) to aim for the mid- to high-normal range (50–70 ng/mL specified by 69% [59.6%–77.6%] of respondents; >70 ng/mL specified by 20% [11.9%–27.3%] of respondents).

Patients who had become pregnant while on DMT would be counseled to discontinue therapy (79% [71.6%–87.2%]). Use of DMT during breastfeeding was not supported (75% [67.2%–83.8%]). Oral cannabis/medical marijuana pills were not prescribed for patients (83% [75.2%–89.8%]).

DISCUSSION

The surveys identified several key themes relating to the diagnosis and treatment of patients with RIS, CIS, or RRMS. In our survey, LP appears to play a more important role in assessments and treatment decisions in RIS than in CIS, whereas treatment decisions are more dependent on clinical symptoms. This observation from practicing physicians is of note in light of findings from several studies that have indicated that the presence of oligoclonal bands in CSF from CIS patients is predictive of conversion to clinically definite MS (CDMS).^{5–7} MRI appears to play an increasingly important role in treatment decisions, with consensus on initiating treatment in a patient with RIS and 2 or more Gd+ lesions. Additionally, spinal MRI is viewed as having increasing relevance, with consensus that these scans are an integral part of the diagnostic evaluation of RIS and CIS. This is in keeping with published evidence that spinal cord MRI may increase the sensitivity of detecting conversion to CDMS⁸ and that spinal cord lesions are an important independent predictor of symptom onset in patients with RIS.^{9,10}

The percentage of physicians who would treat patients with RIS increased from 10% in 2011 to 26% in 2014. Although this 1.6-fold increase was not significant ($p = 0.0664$), it is indicative of physicians' choosing to treat patients at earlier stages of the disease. In patients with CIS, there was strong evidence of earlier use of more aggressive therapy, as fewer physicians would now prescribe first-line treatment with IFN- β or GA ($p < 0.0001$). This is in accordance with accumulating evidence that conversion of CIS to CDMS can be delayed with early treatment.^{11,12}

The choice of treatment also appeared to be tailored to level of disease severity: patients with indications of an aggressive disease course, irrespective of diagnosis, would be prescribed an oral or IV treatment immediately. Despite this, injectable therapies still have an important role, with the majority of respondents initially employing such therapies to treat patients with CIS and ≥ 2 nonenhancing T2 lesions. However, the emergence of oral therapies has had a noteworthy effect on prescribing practices, particularly as alternatives for patients with a suboptimal response to other treatments.

The finding that a majority of physicians would change therapies in clinically stable patients with new T2-hyperintense lesions is consistent with a study that showed new T2 lesions during IFN- β treatment was an important predictor of poor long-term response to therapy.^{13,14}

Despite the large number of consensus findings, several areas of apparent contention remain. These include the appropriateness of treating patients with RIS and no radiologic evidence of acute inflammatory activity, the need for washout periods when transitioning between therapies, and the question of whether treatment needs to be continued indefinitely. Additionally, while the survey showed that vitamin D levels are considered important, consistent with findings that low levels early in the disease course are a strong risk factor for disease progression,¹⁴ there was uncertainty over the precise levels of vitamin D that should be targeted.

The findings of this study may offer insights into harmonizing MS care, particularly in those areas where there is a lack of consensus, and may help to identify areas where more information or guidance is required. Although the results from this study are restricted to a relatively small number of neurologists based in MS clinics in the United States, these results represent the first steps in the potential establishment of a more uniform approach to treatment of patients with MS in the United States, without departing from the principle that each patient needs to be treated individually.

REFERENCES

1. Salhofer-Polanyi S, Leutmezer F. Contemporary treatment options for relapsing-remitting multiple sclerosis. *Drugs Today* 2014;50:365–383.
2. Tornatore C, Phillips JT, Khan O, Miller AE, Barnes CJ. Practice patterns of US neurologists in patients with CIS, RRMS, or RIS: a consensus study. *Neurol Clin Pract* 2012;2:48–57.
3. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995;311:376–380.
4. Hsu CC, Sandford B. The Delphi technique: making sense of consensus. *Pract Assess Res Eval* 2007;12:1–8.
5. Ignacio JJ, Liliana P, Edgardo C. Oligoclonal bands and MRI in clinically isolated syndromes: predicting conversion time to multiple sclerosis. *J Neurol* 2010;257:1188–1191.
6. Ferraro D, Simone AM, Bedin R, et al. Cerebrospinal fluid oligoclonal IgM bands predict early conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome. *J Neuroimmunol* 2013;257:76–81.
7. Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. *J Neurol Neurosurg Psychiatry* 2013;84:909–914.
8. Pericot I, Tintoré M, Grivé E, Briev L, Rovira A, Montalbán X. Conversion to clinically definite multiple sclerosis after isolated spinal cord syndrome: value of brain and spinal MRI. *Med Clin* 2001;116:214–216.
9. Okuda DT, Mowry EM, Cree BA, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. *Neurology* 2011;76:686–692.
10. Okuda DT, Siva A, Kantarci O, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. *PLoS One* 2014;9:e90509.
11. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. *Am J Manag Care* 2013;19:s321–s331.
12. Brownlee WJ, Miller DH. Clinically isolated syndromes and the relationship to multiple sclerosis. *J Clin Neurosci* 2014;21:2065–2071.
13. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. *Eur J Neurol* 2009;16:1202–1209.
14. Ascherio A, Munger KL, White R, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol* 2014;71:306–314.

Received May 29, 2015. Accepted in final form February 16, 2016.

AUTHOR CONTRIBUTIONS

CT, JTP, OK, AEM: study design, questionnaire development, interpretation of data, drafting and revising the manuscript for important intellectual content. MSH: analysis and interpretation of data, drafting and revising the manuscript for important intellectual content.

ACKNOWLEDGMENT

The authors thank Rohit Baskhi, MD, of Harvard Medical School, Boston, MA, and Asif Ally, RPh, of CVS Caremark, Hunt Valley, MD, for their contributions to the steering committee discussions and support of this study; the individual respondents who participated in this survey; and Joshua Safran of Infusion Communications, funded by Biogen, for copyediting the manuscript.

STUDY FUNDING

Biogen convened a steering committee to develop the content of this article and paid committee members for their participation. In addition, Biogen paid honoraria for survey participation and provided funding for study logistics and editorial support. Biogen reviewed drafts and had input into the development of the surveys, reviewed the manuscript, and provided feedback on the manuscript to the authors. The authors had full editorial control of the surveys and manuscript and provided their final approval of all content.

DISCLOSURES

C. Tornatore serves on scientific advisory boards for Biogen Idec and Novartis; serves on speakers' bureaus for Biogen Idec and Genzyme; and receives research support from Biogen Idec. J.T. Phillips has received speaker honoraria from Acorda, Biogen Idec, Genzyme, and Sanofi and an advisory board honorarium from Merck Serono; serves on speakers' bureaus for Acorda, Biogen Idec, Genzyme, and Sanofi; and receives research support from Biogen Idec and Roche. O.A. Khan serves on scientific advisory boards for Teva Pharmaceuticals, Biogen Idec, National MS Society, and Genentech/Roche; has received funding for travel or speaker honoraria from Teva Pharmaceuticals, Novartis, and Biogen Idec; serves on the Editorial Board of *Journal of Neurological Sciences*; serves as a consultant for Teva Pharmaceuticals, Novartis, Biogen Idec, Roche, Genzyme, and Questcor; serves on speakers' bureaus for Teva Pharmaceuticals, Novartis, and Biogen Idec; and receives research support from Teva Pharmaceuticals, Novartis, Biogen Idec, Genzyme, Roche, NIH, National MS Society, DMC Foundation, and Sastry Foundation. A.E. Miller serves as a consultant/on scientific advisory boards for Genzyme/Sanofi-aventis, Biogen Idec, GlaxoSmithKline, EMD Serono, Teva Neuroscience; Merck Serono, Novartis, ONO, Acorda, Nuron Biotech, Mallinckrodt (Questcor), AbbVie, Alkermes, Roche/Genentech, and Caremark (Accordant Health Services); has received funding for travel to advisory board meetings from Genzyme/Sanofi-aventis, Biogen Idec, EMD Serono, Novartis, Acorda, and Roche/Genentech; receives a stipend as *Continuum Audio* Editor; serves on a speakers' bureau for Biogen Idec (only for an unbranded disease awareness program); receives research support from Acorda, Novartis, Roche, Mallinckrodt (Questcor), Genzyme/Sanofi-aventis, Genentech, and Biogen Idec; and has participated in medico-legal cases. M. Hughes serves as Senior Scientific Director for Infusion Communications Inc., which has received funding from the study sponsor Biogen Idec. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Related articles from AAN physician and patient resources

Neurology® Clinical Practice

Disease-modifying therapies for nonrelapsing multiple sclerosis: Absence of evidence does not constitute evidence of absence

December 2013;3:515-518.

Disease-modifying therapies for nonrelapsing multiple sclerosis: Costs and benefits of medical intervention

December 2013;3:510-514.

Continuum® ● ContinuumJournal.com

Switching or Discontinuing Disease-Modifying Therapies for Multiple Sclerosis

June 2016;22:851-863.

New Approaches to the Diagnosis, Clinical Course, and Goals of Therapy in Multiple Sclerosis and Related Disorders

June 2016;22:723-729.

Neurology Today® ● Neurotodayonline.com

Fifteen Years of Publication: Then and Now: Multiple Sclerosis: New Therapies, New Targets, and New Approaches to Treatment

June 9, 2016;16:27-31.