Perspectives for Managed Care Organizations on the Burden of Multiple Sclerosis and the Cost-Benefits of Disease-Modifying Therapies

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ABSTRACT

Disease-modifying therapies (DMTs) are a core component of multiple sclerosis (MS) management. Given current constraints on health care expenditures, the relative cost-effectiveness of these therapies needs to be considered when making treatment decisions. The objective of this article is to review the burden of illness of MS, discuss the cost-effectiveness data for DMTs, and summarize the implications for payers.

For the burden of illness in MS, a retrospective analysis of managed care administrative data from the IMS LifeLink Health Plan Claims Database was performed. Data from claims submitted for patients with confirmed MS (ICD-9-CM code 340) over a period of 1 year (2009) were analyzed. A literature review was conducted to put these data into perspective.

The retrospective analysis determined that the mean annual cost of treating MS in the United States in 2009 was $23,434, which varied according to the presence of comorbidities/complications. Overall, DMTs accounted for 69% of the total costs of managing the disease. According to the literature review, the typical first-line DMTs (interferon beta [IFNβ] formulations and glatiramer acetate [GA]) are generally associated with incremental cost-utility or cost-effectiveness ratios in excess of $100,000 per quality of life year gained. Natalizumab may have cost benefits over other agents in patients with more aggressive disease. According to the available data, studies indicate that DMT cost-effectiveness (specifically cost per quality-adjusted life years) appears to improve with treatment initiation during the early stages of the disease.

In relapsing-remitting MS, there is currently little evidence to differentiate between the DMTs that are typically used first-line (IFNs and GA) based on cost-effectiveness or cost-utility studies. Presently, optimal therapy decisions for DMT-naïve patients are likely to be made individually based on patient and provider preference, adherence, and medication risk-benefit profiles. For patients with more advanced disease, natalizumab appears to have greater efficacy and to be more cost-effective than other agents.

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Summary Points Presented in this Article

- Multiple sclerosis (MS) is a progressive inflammatory and degenerative autoimmune disease of the central nervous system. Most individuals are diagnosed with MS between 20-40 years of age, and there is currently no cure for MS.
- Both pharmacologic and nonpharmacologic interventions are used to manage MS. Disease-modifying therapies (DMTs) are a core component of the pharmacological management of this disease.
- Continuous therapy for MS results in substantial health care expenditures.
- This report presents a retrospective analysis of the cost burden of illness with MS, reports the results of an assessment of the cost-effectiveness of injectable DMTs for MS, reviews the impact of MS on patient work productivity, and summarizes the implications for the managed care audience.

Summary Points Presented in this Article *(continued)*

- According to the retrospective analysis, DMTs account for 69% of the total cost to treat MS in the United States and are associated with high incremental cost-effectiveness ratios ranging from $20,000 to more than $1 million per quality of life year gained. In line with efficacy findings, cost-effectiveness is improved by initiating treatment in early disease stages.
- In relapsing-remitting MS, there is currently little evidence to differentiate between the DMTs that are typically used first-line (interferon betas and glatiramer acetate) based on cost-effectiveness or cost-utility studies.
- Optimal therapy decisions for DMT-naïve patients are likely to be made individually based on disease presentation, patient and provider preference, adherence, and medication risk-benefit profiles.

Multiple sclerosis (MS) is a progressive inflammatory and degenerative disease of the central nervous system (CNS) that is thought to be autoimmune in nature. Most individuals diagnosed with MS experience their first clinical symptoms between 20-40 years of age.[1] Initial signs of illness may include weakness, sensory symptoms, ataxia, visual symptoms, diplopia, and vertigo.[2] These symptoms intensify and abate with relapses or exacerbations separated by periods of stability. Over time, these symptoms accumulate and persist, and other negative effects arise such as bowel and bladder dysfunction, fatigue, muscle spasms, speech disorders, memory loss, and other neuropsychiatric signs.[2] Ultimately, these effects become increasingly permanent, resulting in sustained disability; reductions in quality of life; a decline in work productivity; and considerable costs to the individual, family, and society.[3-6] Given the typical early age of MS onset, a profound burden of this disease is borne by patients and their families over many years.

Managing MS requires both pharmacologic and nonpharmacologic (e.g., physical therapy, occupational therapy, medical devices, and counseling) interventions to control symptoms and delay disease progression and accumulation of disability. Disease-modifying therapies (DMTs) are a core component in the pharmacologic management of MS. Of the DMTs, interferon beta (IFNβ) formulations and glatiramer acetate (GA) have generally been regarded as the mainstay of first-line treatment in patients experiencing a first neurologic episode (known as clinically isolated syndrome [CIS]) and in those with relapsing-remitting MS (RRMS).[7] These immunomodulatory first-line DMTs delay conversion to clinically definite MS (CDMS) in

patients with CIS.[8-12] Although head-to-head clinical trials are lacking in this patient population, the adjusted reductions in the risk of CDMS were generally similar with GA, IFNβ-1a, and IFNβ-1b (ranging from 35% with subcutaneous [SC] IFNβ-1a to 55% with intramuscular [IM] IFNβ-1a over 2 to 3 years).[8-12] However, SC IFNβ-1a has not yet demonstrated efficacy to the standard required from the U.S. Food and Drug Administration (FDA) for an approved indication for use after CIS.[10] Data for patients with CIS are not currently available for the other FDA-approved DMTs: natalizumab (a monoclonal antibody that targets the α4 subunit of α4β1 and α4β7 integrins), mitoxantrone (a cytotoxic agent with immunosuppressive and immunomodulatory properties), or fingolimod (a recently introduced sphingosine 1-phosphate receptor modulator).

All approved DMTs (IFNβs, GA, natalizumab, fingolimod, and mitoxantrone) have demonstrated efficacy in patients diagnosed with RRMS. In pivotal studies in patients with RRMS, use of these agents significantly decreased annualized relapse rates, with most also reducing disability progression rates versus placebo.[13-19] In general, the available data on the efficacy of DMTs in secondary progressive MS (SPMS) are not as conclusive as data in patients with RRMS, and no agent to date has proven benefits in primary progressive MS.

Regarding the safety profiles of the DMTs, IFNβ and GA are associated with injection site reactions (ranging from 10%-15% with IM IFNβ-1a, 30%-48% with SC IFNβ-1a, 60%-63% with SC IFNβ-1b, and up to 90% with GA) and flu-like symptoms (ranging from 15% with GA to a mean of 61% with IFNβ formulations), especially during therapy initiation.[14-16,19] These agents have not been associated with secondary malignancies, serious infections, or significant hematologic considerations, although increases in liver enzyme levels and rare cases of severe hepatic failure with IFNβ formulations have been reported.[14-16,19]

With respect to the other agents, fingolimod, natalizumab, and mitoxantrone currently require close patient monitoring. In clinical trials, fingolimod 0.5 milligram (mg) has been associated with bradycardia (1%-2%), atrioventricular block (0.5%), leukopenia (3%), lymphopenia (3.5%), increased risk for certain infections (e.g., 10% incidence of lower respiratory tract infections in one trial), macular edema (0-0.5%), and hepatic effects (6%-16% incidence of raised liver enzyme levels).[13,20] All patients initiated on fingolimod must be observed for signs and symptoms of bradycardia for at least 6 hours after their first dose. Patients at higher risk because of a coexisting medical condition or certain concomitant medications should be observed overnight with continuous electrocardiogram (ECG) monitoring.

Natalizumab use is associated with a risk for developing progressive multifocal leukoencephalopathy (PML), a rare, opportunistic brain infection caused by the John Cunningham virus (JCV),[21] that can result in severe disability or death. As of February 29, 2012, PML incidence among patients on natalizumab ranged from approximately 0.09/1,000 (95% confidence interval [CI] 0 to 0.48) to 11/1,000 (95% CI=8.3-14.5), depending on an individual's anti-JCV antibody positive status, prior immunosuppressant use, and duration of natalizumab exposure.[22] A commercial assay that detects anti-JCV antibodies in human serum and plasma has recently become available.[21] This assay, together with the assessment of other recognized risk factors, enables clinicians to stratify patients who may be at higher and lower risk of developing PML.[23] The reported incidence of PML in patients who tested negative for anti-JCV antibodies prior to PML onset is 0.11/1,000, or greater than 20-fold lower than the PML incidence in patients who are positive for anti-JCV antibodies.[24] As a consequence of the risk of PML, the FDA indication currently recommends natalizumab as monotherapy for the treatment of relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations in patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy, although its recommended use is not restricted to second-line therapy.[22]

Mitoxantrone therapy for MS is restricted by the FDA to patients with secondary progressive MS, progressive-relapsing MS, and worsening RRMS. This approval was based on the results from a pivotal trial of mitoxantrone for MS conducted in patients with more advanced disease[17] and on a lifetime dose restriction for mitoxantrone due to the drug's toxicity, which has been associated with blood cancers, clinically significant myelosuppression, increased risk of infections, and potentially fatal cardiotoxicity.[25]

Given the current availability of several DMTs for MS and the demands that continuous therapy places on health care expenditure, the relative cost-effectiveness of these options must be regularly evaluated, and the results of these evaluations can become a guide to treatment decisions.

The main objectives of this article are to summarize the burden of illness associated with MS, to discuss the per-patient costs associated with individual DMTs that are approved by the FDA for treating MS, to provide an overview of cost-utility and cost-effectiveness data for these therapies, and to discuss the impact of MS on work productivity and absenteeism. We will also describe the gaps in our current knowledge on these topics and their potential implications for payers.

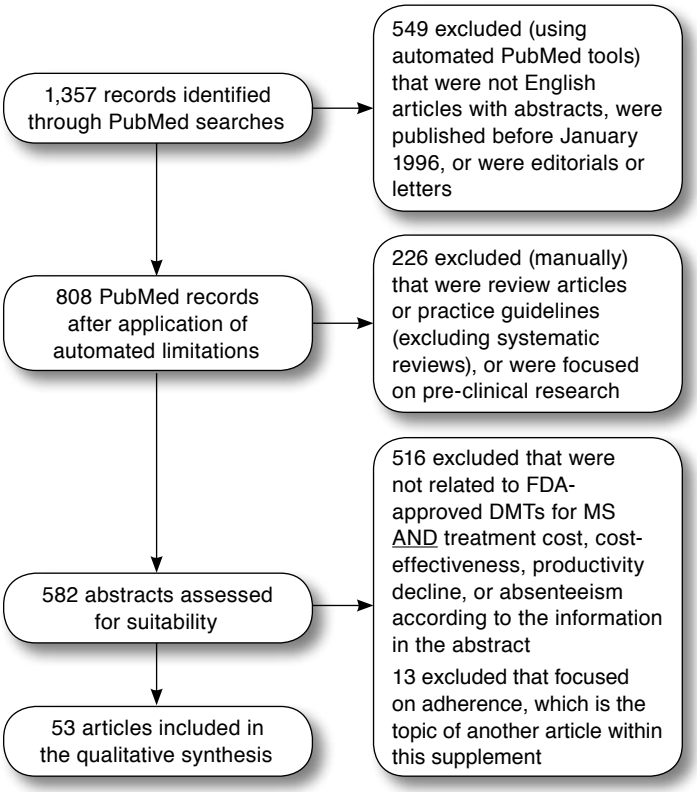
Methods

This article presents the results of a descriptive, retrospective report of patient-level medical and pharmacy claims data in the United States, supplemented by a literature review.

Total Resource Utilization Benchmarks Analysis

Source Data. Patient-level administrative claims data were obtained from the IMS LifeLink Health Plan Claims Database, a large data warehouse of administrative claims that has been used for previous analyses of data on patients with MS.[26-28] At the time these analyses were conducted, the database

FIGURE 1 Flow Chart of Article Selection for Locating Articles on the Cost and Cost-Effectiveness of Disease-Modifying Therapies for the Management of Multiple Sclerosis



DMT = disease-modifying therapies; FDA = U.S. Food and Drug Administration; MS = multiple sclerosis.

contained data from more than 100 private and public (Medicare and Medicaid) health care plans across the United States, representing more than 60 million unique patients. Additional data elements from the database used in this analysis included patient characteristics such as geographic region, age and gender, insurance type (e.g., health maintenance organizations [HMOs], preferred provider organizations [PPOs]), and payer type (e.g., commercial, self-insured, Medicare risk).

Software and Methods for Aggregating and Organizing Data and Patient Selection. The IMS/PharMetrics patient-centric data were organized and grouped using Symmetry Episode Treatment Group (ETG) software (Ingenix, Eden Prairie, MN), a patented illness-classification and episode-building software application. The widely recognized ETG methodology is used by more than 400 managed health plans nationwide.[27,29,30] This software is described in detail elsewhere.[31,32]

Patients were selected for study inclusion if they had 12 months of continuous eligibility for 2009, valid data for age and gender, and evidence of treatment for MS. For selection, patients were identified by the presence of an ETG-defined episode of care and specific *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding using the ETG codes ETG 149 (inflammation of the CNS, with surgery) and ETG 150 (inflammation of the CNS, without surgery). Only patients with these ETG-based episodes and a diagnosis code for MS (ICD-9-CM code 340.xx) were included.

Once selected, ETG data were stratified using the Total Resource Utilization (TRU) Benchmarks process (Gemini Healthcare, Westbrook, CT, www.diseasebenchmarks.com). The dataset captures information across the continuum of patient care and organizes it into consistently formatted, episode-based benchmarks for comparison. TRU Benchmarks reports episode-based metrics of costs, units of use, and services utilized. Example benchmarks used previously for TRU Benchmarks studies in MS and other diseases include the drug therapy used, patient demographics, the presence and number of complications and comorbidities, episode costs, and resource utilization across all health care service categories.[27,29,33,34]

Literature Search Strategy. To locate articles on cost and cost-effectiveness, the following targeted (nonsystematic) literature review was performed using PubMed on September 15, 2011: (Health Care Economics and Organizations [MeSH Major Topic] OR costs OR cost OR cost-effectiveness OR employ OR employment OR employee OR absenteeism OR absentee) AND multiple sclerosis OR "multiple sclerosis/economics" [MeSH Terms]. Overall, 1,357 articles were selected using this search strategy (Figure 1). The search was limited to English language articles with abstracts published since IFNβ-1a became available for the treatment of MS, from January 1996 to the present. Editorials and letters were excluded. After applying these limitations using the automated limit function in PubMed, and then manually excluding review articles (aside from systematic reviews) and articles focused on pre-clinical research, the search yielded a total of 582 articles. Following an evaluation of abstracts, 53 final articles were incorporated that contained information on FDA-approved DMTs and treatment cost, cost-effectiveness, productivity decline, or absenteeism. A further 43 references were included to supplement the introduction, methods, and "gaps in knowledge" sections of the article based on awareness of the literature and additional searching where appropriate.

Results

Overall Cost of Illness

Total Resource Utilization Benchmarks Analysis. The baseline characteristics for the 31,401 patients included in the MS Benchmarks analysis are summarized in Table 1. In line with MS in the U.S. population, the majority of patients (77%) were women, and nearly one-half (44%) were between 26 and 39 years of age.[35,36]

TABLE 1 Baseline Characteristics of Patients Included in the Total Resource Utilization Benchmarks Analysis

Baseline Characteristics	n	Overall %
Demographics		
Age, years		
18-25	667	2
26-39	13,880	44
40-64	13,762	44
≥65	3,092	10
Total	**31,401**	**100**
Gender		
Female	24,053	77
Male	7,348	23
Comorbidities and conditions (≥10% overall)		
Hyperlipidemia	9,690	31
Hypertension	9,603	31
Asthenia	7,944	25
Depression	6,672	21
Urinary tract infection	5,310	17
Burning, numbness, tingling	5,221	17
Thyroid disorder	4,826	15
Low back pain	4,537	14
Headache	3,809	12
Abnormality of gait	3,417	11
Malignancy	3,398	11
Diabetes	3,221	10
Dizziness	3,078	10

TABLE 2 Health Care Services Utilization by Patients with MS: Findings from the Total Resource Utilization Benchmarks Analysis

Service Category	Patients with Use[a] (n)	Episodes with Use[b] (%)	All Episodes,[b] Mean Units of Use[c]	All Episodes,[b] Mean Costs ($)[d]	Percentage of Total Costs
Inpatient ancillary	1,490	5	0.80	549	
Inpatient facility	795	3	0.05	452	
Inpatient management	1,078	3	0.24	73	
Inpatient surgical	183	<1	0.01	8	
Inpatient total	**1,539**	**5**	**1.10**	**1,082**	**5**
Outpatient ancillary	24,106	77	10.75	4,291	
Outpatient management	25,406	81	4.14	662	
Outpatient surgical	1,906	6	0.15	77	
Outpatient total	**29,040**	**93**	**15.04**	**5,030**	**22**
Emergency room	**2,629**	**8**	**0.84**	**310**	**1**
Pharmacy: DMTs	17,113	55	4.80	16,104	
Pharmacy: other classes	15,816	22	3.75	909	
Pharmacy total	**24,274**	**77**	**8.55**	**17,013**	**73**
Total episode costs		**—**	**—**	**23,434**	**100**

[a]*Patients with use: patients utilizing at least 1 coded, clinically related service for MS care.*

[b]*Episodes with use: average number of coded, clinically related services utilized by a patient for MS care during 1 calendar year.*

[c]*Units of use: average counts of interactions and services patients incurred during an episode of care. Numbers represent annual data.*

[d]*Costs: average cost per unit of use, excluding payment made by the patient for service utilization.*

DMT = disease-modifying therapy; MS = multiple sclerosis.

According to the findings from this analysis, in 2009, the average annual total for MS-related health care costs in the United States was $23,434 (Table 2). This amount is higher than a previous report[5] and is most likely due to differences in prior DMT use between the 2 populations analyzed and how the ETG software captures claims. Cost varied by the type of comorbidities/complications, with patients experiencing ataxia ($31,483), abnormality of gait ($31,175), muscle weakness ($29,104), spasms ($28,843), urinary incontinence ($28,561), and optic neuritis ($28,353) incurring the largest costs.

The annual costs per patient for managing MS in the MS Benchmark analysis came from pharmacy costs (73%; $17,013) and outpatient visits (21%; $5,030), inpatient services (5%; $1,082), and emergency room visits (1%; $310; Table 2). The types of pharmacotherapies used overall by patients in the analysis included DMTs (51%), migraine agents (46%), antidepressants (43%), narcotic analgesics (39%), corticosteroids (33%), antispastics (30%), anticonvulsants (29%), nonsteroidal anti-inflammatory drugs (NSAIDS; 22%), and benzodiazepines (22%). Despite the widespread use of other drugs, DMTs accounted for 95% ($16,104) of the total annual pharmacy costs per patient and 69% of the total costs for managing MS. Of the remaining pharmacotherapies, no single drug class accounted for more than 1.5% of the total pharmacy costs.

Literature Search. The economic burden of MS is considerable due to the interventions, diagnostics, and monitoring required for MS as well as to the loss in patient productivity and employment.[5,37-39] It has been estimated that the total lifetime cost per patient with MS is $2.2 million in 1994 U.S. dollars, which translates to $4.1 million in 2010 dollars.[38,40] For newly diagnosed patients, the all-cause health care costs are estimated to average $18,829 in the first year alone compared with an average of $4,038 annually for a healthy comparison group,[5] and this figure can rise substantially. In a recent review, Sharac et al. (2010) found that cost ranged from $6,603 to $77,938 per person with MS per year (2008 values), with amounts varying by disease severity and country of residence.[39] According to this review, in the United States, the cost of MS per person ranged from $12,879 to $48,839.[39] These observations are generally in agreement with findings from the MS Benchmarks analysis, which showed that costs for MS care were highest for patients with certain complications/comorbidities.

As previously reported, direct costs related to MS include inpatient services, emergency room visits, physician visits, laboratory and radiology services, other outpatient services, and pharmacologic interventions.[4,5,39,41] However,

TABLE 3 *Average Annual Costs (U.S. Dollars) Associated with the Use of Disease-Modifying Therapies: Findings from the Total Resource Utilization Benchmarks Analysis*

		IM IFNβ-1a (n = 4,485)		SC IFNβ-1a (n = 3,130)		IFNβ-1b (n = 2,059)		GA (n = 6,969)	
Inpatient	Mean [SD]	809	[10,503]	1,288	[11,730]	793	[5,778]	1,285	[10,747]
	Median [min/max]	-	[-/425,679]	-	[-/356,616]	-	[-/120,228]	-	[-/331,825]
Outpatient	Mean [SD]	4,205	[7,653]	5,657	[12,637]	4,623	[7,740]	5,022	[8,463]
	Median [min/max]	1,775	[-/139,942]	2,997	[-/381,430]	2,054	[-/114,277]	2,454	[-/168,168]
Emergency room	Mean [SD]	320	[2,495]	336	[2,085]	383	[2,412]	338	[1,996]
	Median [min/max]	-	[-/108,025]	-	[-/71,192]	-	[-/52,486]	-	[-/83,220]
Pharmacy	Mean [SD]	30,671	[16,639]	29,033	[14,994]	30,976	[18,404]	29,534	[17,439]
	Median [min/max]	30,795	[-/269,747]	30,651	[-/195,437]	30,226	[-/282,453]	30,210	[-/574,099]
Product specific	Mean [SD]	28,895	[16,132]	25,970	[13,884]	28,814	[17,037]	27,538	[16,905]
	Median [min/max]	29,720	[0/211,072]	28,208	[0/133,696]	29,180	[0/236,864]	28,700	[0/573,824]
All other pharmacy	Mean [SD]	1,776	[7,448]	3,062	[9,379]	2,162	[7,733]	1,996	[7,086]
	Median [min/max]	19	[-/259,797]	85	[-/186,503]	72	[-/195,765]	53	[-/124,643]
Total annual costs	Mean [SD]	**36,006**	**[21,002]**	**36,314**	**[22,840]**	**36,775**	**[21,442]**	**36,179**	**[22,569]**
	Median [min/max]	**34,198**	**[-/435,138]**	**34,892**	**[-/432,171]**	**34,462**	**[-/323,924]**	**33,942**	**[-/575,788]**

IFNβ = interferon beta; IM = intramuscular; min/max = minimum/maximum; GA = glatiramer acetate; SC = subcutaneous; SD = standard deviation.

the MS Benchmarks analysis did not include indirect societal costs such as reduced productivity, absenteeism, early retirement, and additional types of earning losses, which have been accounted for in other studies.[4,39] Kobelt et al. (2006) found that 37% of total costs were due to production losses or informal care.[37] Therefore, the Total Resource Utilization Benchmarks analysis may underestimate the total economic burden of MS ($23,434 in 2009 values) when compared with other U.S.-based studies that have included societal costs ($45,284 to $52,830 in 2008 values).[37,40] This difference also likely explains why studies such as the one by Kobelt et al.[37] suggest that DMTs account for a lower proportion of the total MS costs relative to the MS Benchmarks analysis (34% vs. 69%, respectively) and to another U.S. study that only included direct costs[28] (34% vs. 71%-76% [depending on the DMT], respectively). Nevertheless, whichever study is considered, DMTs make up a large portion of the total costs of MS. It is therefore important to consider which DMTs are most likely to deliver optimal cost-effectiveness.

Costs for Patients with MS by DMT

Total Resource Utilization Benchmarks Analysis. According to the MS Benchmark analysis, patient groups using each of the main first-line DMTs (GA and IFNβ formulations) had similar average annual costs specific to the treatment of MS. There was no practical difference among the 4 studied DMTs in average annual medical costs. Average costs ranged narrowly from $36,006 for patients on intramuscular (IM) IFNβ-1a to $36,775 for patients on subcutaneous IFNβ-1b (Table 3). Comparisons across DMT treatment groups showed that IM IFNβ-1a had the lowest inpatient, outpatient, and emergency room costs and the lowest cost of concomitant pharmacy treatments (Table 3; statistical testing not performed).

Literature Search. Previously, studies have evaluated the "real-world" costs of DMTs in the past 5 years in the United States.[5,27,34,42-46] As seen in the MS Benchmarks analysis, several reports stated that there were no substantial differences between the costs of the studied DMTs.[45,47,48] Bell et al. (2007) estimated that the total costs per patient over a lifetime were $352,760, $364,267, $377,996, and $358,509 for GA, IM IFNβ-1a, SC IFNβ-1a, and SC IFNβ-1b, respectively.[45] Conversely, several other studies concluded that the costs may be different among the DMTs.[27,42,44,46] Prescott et al. (2007) found that the annual costs of GA ($16,928) were lower than those of IM IFNβ-1a, IFNβ-1b, and SC IFNβ-1a ($17,987, $19,616, and $22,557, respectively; all $P < 0.001$).[27] Data for this study were reported in 2004; therefore, drug cost comparisons may no longer be accurate. However, similar findings showing lower total costs with GA were reported elsewhere.[42,44]

Regarding natalizumab, which was not evaluated in the current MS Benchmarks analysis, a study indicated that the annual costs of this DMT (in 2008 U.S. dollars) are higher than for typical first-line agents (IFNβs and GA).[46] However, data from a new decision analytic model developed to estimate the incremental cost per relapse avoided with natalizumab and fingolimod from a U.S. managed care payer perspective showed that estimated 2-year treatment costs in the United States are lower for natalizumab than the recently introduced DMT fingolimod ($86,461 vs. $98,748, respectively).[49]

While evaluating the total costs to treat patients with various DMTs is useful, it is more important to evaluate these costs as they relate to effectiveness. In this regard, the numerous published analyses of the cost-effectiveness and cost-utility of DMTs for MS are summarized below.

Cost-Utility and Cost-Effectiveness Analyses of DMTs

Costs Per Quality-Adjusted Life Year. Certain institutions, such as the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, use quality-adjusted life years (QALYs) to compare different drugs and measure their clinical effectiveness and use cost per QALY as a measure of cost-effectiveness.[50] In the United States, a cost per QALY value of $50,000 is sometimes used as a threshold for cost-effectiveness.[45,48] Numerous studies have assessed the cost per QALY of the approved DMTs for MS, aside from fingolimod (Table 4).[45,47,48,51-66] These studies arrived at widely different estimates, with costs per QALY varying from around $20,000 to over $1 million.

It is difficult to make comparisons across these studies because of differences in study time horizons, data inputs, geographical locations, utility values, and associated assumptions, all of which can have a large influence on model results.[39] The trend was for the studies to show high cost per QALY estimates, indicating that by this measure DMTs may not be cost-effective. However, consideration of only direct medical costs has a number of limitations, most notably not always considering social values such as absenteeism, productivity, and impact on family and caregivers.[50] The impact of DMTs on employment and absenteeism in patients with MS is addressed below.[50]

Multiple analyses comparing IFNβ formulations and GA have been published (Table 4) using cost per QALY, but conflicting results between the studies make it difficult to conclusively determine whether or not there are any differences in cost-effectiveness among these drugs.[39,45,47,56] Regarding natalizumab, in 2 analyses comparing different treatments, this DMT appeared to have an improved cost per QALY relative to the IFNβs and GA.[55,58] This was mostly due to the efficacy benefits observed with natalizumab in clinical trials of patients with highly active RRMS and SPMS. Another economic model reporting increased patient benefits with natalizumab or GA compared with symptom management (increased years in Expanded Disability Status Scale [EDSS] 0.0-5.5, years relapse-free, and QALYs) also suggested a similar or slightly improved lifetime cost per QALY for GA versus natalizumab in patients with RRMS when the impact of discontinuation and antinatalizumab antibodies was also considered.[48] However, the study was limited by the assumptions made for cost estimates and utility weights associated with EDSS progression because of a lack of data on change in clinical efficacy and discontinuation over time for patients receiving natalizumab. Similarly, another analysis showed an improvement in the cost-effectiveness of mitoxantrone versus IFNβ-1b when used to treat patients with SPMS or progressive-relapsing MS.[62]

Several studies summarized in Table 4 suggest DMT cost-utility estimates improve when DMTs are given earlier in the disease course.[47,63,64] Lazzaro et al. (2009) found that treatment with IFNβ-1b after CIS is highly cost-effective compared with delaying treatment until a patient has CDMS (incremental cost per QALY: €2,574.94).[64] In patients with CDMS, Tappenden et al. (2009) found that the cost of IFNβ-1b per QALY gained was considerably better for treating RRMS versus treating both RRMS and SPMS ($91,515 to $168,793 vs. $122,202 to $312,344).[63] Finally, Noyes et al. (2011) showed that for all evaluated agents, early treatment initiation with DMTs (EDSS score 2.0-2.5) improved the cost of DMT therapy per QALY gained compared with waiting to start a DMT until after patients had reached a higher rate of disability (EDSS score 3.0-4.0).[47]

Costs Per Relapse Avoided. DMT costs may be partially offset by preventing relapses.[4] Treating the symptoms associated with relapses costs, at 2002 price levels, between $243 for the mildest cases and $12,870 for severe relapses that required hospitalization.[67] Consequently, a number of studies have investigated the cost of DMTs per each relapse avoided.[46,47,60,66,68-71] Here, the focus is on comparative studies that examined differences in cost per relapse avoided among the various DMTs.

A study that included patients with both RRMS and SPMS found that the costs per relapse-free year were similar among the SC IFNβ formulations and GA ($188,973 to $216,426) and higher with IM IFNβ-1a ($303,339).[47] In patients with RRMS, a German model indicated that SC IFNβ-1a (€51,250) is more cost-effective than IM IFNβ-1a (€133,770), GA (€71,416), or IFNβ-1b (€54,475) in terms of cost per relapse avoided.[71] In contrast, a Markov model using long-term clinical RRMS data determined that the incremental cost per relapse-free year was comparable for IM IFNβ1-a, IFNβ-1b, and GA ($17,599 to $24,327), but slightly higher with SC IFNβ-1a ($32,207).[45] Finally, in another analysis of these 4 agents, which included data from patients with RRMS who had received treatment for at least 2 years, the estimated costs per relapse avoided were similar among IM IFNβ-1a ($77,980), SC IFNβ-1a ($80,121), IFNβ-1b ($86,572), and GA ($87,767).[69]

With regard to natalizumab, a model that included data from patients on this DMT, 1 of the IFN formulations, or GA found that the 2-year cost of therapy was highest for natalizumab. However, the cost per relapse avoided was lower for natalizumab ($56,594) relative to the IFNβs and GA ($87,791 to $103,665), which was attributed to its association with fewer relapses.[46] The cost-effectiveness of natalizumab for preventing relapses relative to these DMTs is supported by another analysis.[70] More recently, O'Day et al. (2011) examined the cost per relapse avoided for natalizumab versus fingolimod.[49] Natalizumab was found to be more cost-effective than fingolimod for relapse prevention as a result of its lower costs and apparent greater efficacy in reducing relapses, although head-to-head studies are lacking.

Costs for Prevention of Disability

The ultimate goal for MS treatment should be to prevent the progression of disability for the benefit of patients and society. In terms of burden on society, a systematic review

TABLE 4 *Summary of Results from Economic Evaluation Studies Investigating Cost Per QALY Associated with Disease-Modifying Therapies*

Study (Year Published) Country [Sponsor]	Population (Time Horizon); Perspective	Treatments	Comparators	Results[a]
Bell et al. (2007); United States [Teva Neuroscience][45]	RRMS (lifetime); societal	Symptom management combined with SC GA SC IFNβ-1a SC IFNβ-1b IM IFNβ-1a	Symptom management alone	Cost per QALY (compared with symptom management alone): Symptom management plus SC GA $US258,465 SC IFNβ-1a $US416,301 SC IFNβ-1b $US310,691 IM IFNβ-1a $US303,968
Earnshaw et al. (2009); United States [Teva Neuroscience][48]	RRMS (lifetime); health care and societal	SC GA Natalizumab	Symptom management	SC GA $US496,222 Natalizumab $US606,228
Noyes et al. (2011); United States [National MS Society, University of Rochester, and NIH][47]	RRMS or SPMS (10 years); societal	SC GA SC IFNβ-1a SC IFNβ-1b IM IFNβ-1a	Supportive care	SC GA $US1,763,036 SC IFNβ-1a $US1,255,088 SC IFNβ-1b $US958,738 IM IFNβ-1a $US898,169
Prosser et al. (2004); United States [National MS Society, Harvard Program on the Economic Evaluation of Medical Technology, Harvard Center for Risk Analysis, and the Thomas O. Pyle Fellowship][61]	Newly diagnosed with nonprimary progressive MS (10 years); societal	IM IFNβ-1a SC IFNβ-1b SC GA	No treatment	No treatment dominated both SC IFNβ-1b and SC GA IM IFNβ-1a (compared with no treatment): cost per QALY $US2.2 million for women and $US1.8 million for men
Tappenden et al. (2009); United States [United States Department of Health and Human Services][63]	RRMS and SPMS (50 years); health care	SC IFNβ-1a IM IFNβ-1a SC IFNβ-1b SC GA	Supportive care	Physician-administered IM IFNβ-1a 6 MIU: $US66,082 to $US233,967 Self-administered IM IFNβ-1a 6 MIU: $US60,052 to $US218,206 SC IFNβ-1a 22 μg: $US120,688 to $US199,189 SC IFNβ-1a 44 μg: $US79,002 to $US172,438 SC IFNβ-1b 8 MIU for RRMS: $US91,515 to $US168,793 SC GA 20 mg: $US202,648 to $US316,128 SC IFNβ-1b 8 MIU for RRMS/SPMS: $US122,202 to $US312,344
Touchette et al. (2003); United States [Immunex Corporation][62]	SPMS or progressive relapsing MS (20 years); health care and societal	Mitoxantrone SC IFNβ-1b	Standard supportive care	Mitoxantrone hydrochloride: cost per QALY $US34,317 SC IFNβ-1b: cost per QALY $US228,934
Bose et al. (2001); United Kingdom [None stated][66]	RRMS (8 years); health care	SC GA	Supportive care	Cost per QALY £20,929
Chilcott et al. (2003); United Kingdom [National Institute for Clinical Excellence.][56]	RRMS (all drugs) or SPMS (only IFNβ-1b) (20 years); health care	IM IFNβ-1a 6 MIU/wk SC IFNβ-1a 22 μg/wk SC IFNβ-1a 44 μg/wk SC IFNβ-1b 8 MIU/wk SC GA 20 mg/wk	No treatment	Cost per QALY: IM IFNβ-1a 6 MIU per wk £73,137 SC IFNβ-1a 22 μg per wk £105,718 SC IFNβ-1a 44 μg per wk £124,034 SC IFNβ-1b 8 MIU per wk £86,127 SC GA 20 mg per wk £168,539 SC IFNβ-1b 8 MIU per wk (RRMS and SPMS) £78,722
Forbes et al. (1999); United Kingdom [None stated][57]	SPMS (2.5 years); health care	SC IFNβ-1b	Best practice without IFNβ	Cost per QALY £1,024,667
Gani et al. (2008); United Kingdom [Biogen Idec][58]	Highly active RRMS (30 years); societal	Natalizumab	Best supportive care IFNβ SC GA	Cost per QALY of natalizumab compared with: Best supportive care £8,200 IFNβ £2,300 SC GA £2,000
Nuijten and Hutton (2002); United Kingdom [None stated][59]	RRMS (lifetime); health care and societal	SC IFNβ-1b	Usual care	Health care: cost per QALY £51,582 Societal: cost per QALY £45,641
Parkin et al. (2000); United Kingdom [NHS Health Technology Assessment program][60]	RRMS (5 years and 10 years); health care	SC IFNβ-1b	No treatment	5 years: cost per QALY £328,300 10 years: cost per QALY £228,300

TABLE 4 Summary of Results from Economic Evaluation Studies Investigating Cost Per QALY Associated with Disease-Modifying Therapies *(continued)*

Study (Year Published) Country [Sponsor]	Population (Time Horizon); Perspective	Treatments	Comparators	Results[a]
Phillips et al. (2001); United Kingdom [None stated][65]	RRMS (10/20 years); societal	SC IFNβ-1b	Usual care	10 years: cost per QALY £14,600 20 years: cost per QALY £3,000
Kobelt et al. (2000); Sweden [Schering AG][52]	SPMS (10 years); societal	SC IFNβ-1b	Usual care	Cost per QALY $US39,250
Kobelt et al. (2002); Sweden [Schering AG][53]	SPMS (10 years); societal	SC IFNβ-1b	Usual care	Cost per QALY $US25,700
Kobelt et al. (2003); Sweden [None stated][54]	RRMS or SPMS (10 years); societal	SC IFNβ-1b	Usual care	Cost per QALY €38,700
Kobelt et al. (2008); Sweden [Biogen Idec and Elan Corp.][55]	RRMS or SPMS (20 years); societal	Natalizumab	SC IFNβ-1a IM IFNβ-1a SC IFNβ-1b SC GA	Natalizumab is dominant (costs are €3,830 lower and increase of 0.34 QALYs)
Lazzaro et al. (2009); Italy [Bayer Schering Pharma][64]	CIS/CDMS (25 years); health care and societal	SC IFNβ-1b since CIS diagnosis	SC IFNB-1b since CDMS diagnosis	Cost per QALY €2,574
Iskedjian et al. (2005); Canada [Biogen Idec][51]	CIS (12/15 years); health care and societal	IM IFNβ-1a	Usual care	12 years (health care): cost of 1 year without progressing to MS $Can53,110 15 years (societal): cost of quality-adjusted monosymptomatic life-year $Can189,286

Source: Sharac J, McCrone P, Sabes-Figuera R. Pharmacoeconomic considerations in the treatment of multiple sclerosis.[39]

[a]*All studies are models.*

CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; GA = glatiramer acetate; IFNβ = interferon beta; IM = intramuscular; mg = milligram; MIU/wk = million international units per week; MS = multiple sclerosis; NHS = National Health Service; NIH = National Institutes of Health; QALY = quality-adjusted life year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; µg = micrograms.

Currency: $Can = Canadian dollars; € = euros; £=pounds; $US = U.S. dollars.

demonstrated that the total costs of MS rose significantly with increases in disease severity as measured by EDSS scores. These cost increases were driven by relapses and productivity costs more so than the direct costs of DMTs.[4] Interventions aimed at delaying disease progression may reduce total societal costs by decreasing the need for additional care such as rehabilitation, nursing care, and other caregivers.[4]

Two studies have investigated the costs of DMTs for each year of disability avoided. Brown et al. (2000) found that use of IFNβ-1b for MS prevented 2 years of disability over a 40-year time horizon versus health care without a DMT, with an estimated cost per year of disability avoided of $181,395. However, the study did not consider work absenteeism, lost productivity and patient dependence on care, or the long-term costs of care.[72] Another model analyzing costs for patients with RRMS that considered long-term savings found that treatment with SC IFNβ-1a was cost-effective[73]: treatment with IFNβ-1a in the United Kingdom was estimated to cost £453 per month over 10 years and £222 per month of disability prevented over 20 years. Data were not reported for other DMTs.

Impact of DMTs on Work Productivity and Absenteeism

MS is associated with high unemployment rates, with only 20%-60% of people with MS remaining employed in longitudinal studies.[74-79] This observation is of consequence given that MS affects an estimated 400,000 people in the United States.[35] The North American Research Committee on Multiple Sclerosis (NARCOMS) database, a global registry for MS research, treatment, and patient education, is a probability sampling that contains detailed data submitted confidentially by MS patients. An analysis reported in September 2011 in a congress abstract that evaluated the impact of treatment on employment status[80] found that unadjusted mean 10-year patient employment rates were higher with once-weekly IM IFNβ-1a (55%) than with GA (48%; difference not significant), SC IFNβ (1a or 1b; 42%; $P = 0.015$), or no treatment (33%; $P < 0.001$).[80] Patients receiving DMTs were more likely to be employed after 10 years than untreated patients.

Absenteeism is high for patients who maintain employment. In 1 study, annual absenteeism rates for employees with MS ranged from 2.98 to 8.13 days; total sick time ranged from 7.33 to 20.67 days; and sick-leave costs ranged from $523 to $1,431.[81] While the proportion of patients with MS in any given workforce will be low, those companies that do have employees with this illness may be affected by loss from reduced output while an employee is at work and from absenteeism as well as from extra staffing costs incurred to cover sick leave.[38,82]

DMTs may allow employees to continue working and thus help reduce absenteeism. Several analyses have examined the impact of DMTs on costs and absences due to sick leave.[38,81,83,84] However, these analyses were generally limited by their retrospective designs, small samples sizes, and conflicting results.

Only 1 prospective study has assessed the impact of DMTs on absenteeism.[84] Collectively, these studies generally found benefits of DMTs on reducing the costs associated with absenteeism.[7,16,18,19] One such U.S. study of employees with MS and at least 1 DMT claim versus untreated employees with MS found that the risk-adjusted total annual medical costs ($4,393 vs. $6,187; $P<0.001$) and indirect costs ($2,252 vs. $3,053; $P<0.001$) were significantly lower for employees with at least 1 DMT claim.[43]

With regard to differences between DMTs in MS-associated absenteeism, Brook et al. (2009) found that patients receiving IM IFNβ-1a had lower sick-leave costs ($969 vs. $523, respectively; $P=0.047$) and fewer sick-leave days (2.98 vs. 7.18 days, respectively; $P=0.01$) versus those receiving GA.[81] Similarly, Rajagopalan et al. (2011) reported that patients treated with IM IFNβ-1a demonstrated a significant improvement in the number of missed work days, with a decrease of 1.3 days (from 5.6 to 4.3 days) versus an increase of 2 days (from 2.3 to 4.3 days), in GA-treated patients ($P<0.05$).[38] Only patients receiving IM IFNβ-1a showed a reduction in sick-leave absence days with therapy, while sick leave increased with SC IFNβ-1a, IFNβ-1b, and GA. In contrast, Lage et al. (2006) found that GA, compared with IM IFNβ-1a or IFNβ-1b, was associated with significantly fewer days missed from work for any reason. Compared with those not receiving a DMT, GA, IM IFNβ-1a, and IFNβ-1b were associated with 53.70 ($P=0.003$), 20.73 ($P=0.09$), and 8.28 ($P=0.71$) fewer days away from work, respectively.[83] In a prospective study, GA was associated with a significant improvement in fatigue symptoms and a marked reduction in absence from work compared with patient baseline status.[84]

Overall, these results suggest that DMTs are likely to have a positive impact on employment and work productivity, although it is not possible to conclusively determine if certain DMTs have particular benefits. Furthermore, data are lacking on fingolimod and on natalizumab.

Study Limitations

Several study limitations should be considered when evaluating the study results presented here. The Total Resource Utilization Benchmarks analysis was a retrospective, descriptive study; that the study was not inferential; and that the analyses could not control for potential confounding factors. Also, a targeted rather than systematic literature review was performed, and while an effort was made to collect all relevant studies, certain studies may have been inadvertently excluded from the review. Additionally, the cost-effectiveness analyses were not comprehensively discussed, and the quality of the reports was not assessed.

Gaps in Knowledge: Where Is Future Research Required?

Oral Therapies. A key gap in our current knowledge regarding the cost-effectiveness of current therapies for MS relates to new oral therapies. Fingolimod was recently approved for use in RRMS by the FDA and within Europe and has been shown to produce greater reductions in annualized relapse rates compared with current DMTs (but no difference in disability progression vs. IM IFNβ-1a).[13,20] Further, other oral therapies such as laquinimod, teriflunomide, and BG-12 have recently completed phase 3 trials and may receive future approval. Given that these therapies are administered orally, it is possible that they could be associated with better adherence due to the greater ease of administration and avoidance of injection anxiety that can occur with other DMTs. However, there are currently no studies demonstrating better adherence with oral therapies in MS. Demonstration of improved adherence with oral agents could lead to certain cost advantages versus some injectable therapies (in particular, lower out-of-pocket expenses for patients in the United States).[85]

There are still other uncertainties regarding fingolimod that clinicians and managed care organizations may need to consider. In particular, long-term safety data, monitoring practices, experience with the drug in clinical practice, and cost-effectiveness data are somewhat lacking. Furthermore, the impact of this oral agent on patient work productivity and absenteeism is currently unknown. In terms of medication costs alone, an annual course of fingolimod is more expensive than other agents. Although this direct cost does not consider DMT effectiveness and the benefits of related improvements in patient outcomes, it is of interest that the poster report of a recent Markov risk-benefit model indicated that the net health benefit of treatment, taking into account treatment efficacy and adverse effects, was similar between fingolimod and IM IFNβ-1a over 5 years (3.76 vs. 3.73 QALYs, respectively).[86] Additionally, a recent study indicated that natalizumab is more cost-effective than fingolimod in terms of costs per relapse avoided.[49] However, further cost-effectiveness research is required.

Combination Therapy. MS is a highly heterogeneous disease, and combination therapy strategies that target a range of disease mechanisms might be more effective than agents used as monotherapy. Currently, there is no FDA-approved combination MS therapy regimen. DMTs have been administered in combination with drugs approved for other indications, such as corticosteroids, methotrexate, azathioprine, and cyclophosphamide, with varying degrees of success.[87] With the arrival of oral therapies, it is possible that DMT combination therapy could be used more frequently in MS, particularly since these new agents have different proposed mechanisms of action than the IFNβs and GA. Combining drugs with different mechanisms of action has the potential to produce greater efficacy, increased patient benefits, and improved employment rates. However, drug combinations also have the potential to cause an

increased incidence of adverse events and will lead to greater direct medication costs. Perhaps surprisingly, a recent National Institutes of Health (NIH) study (http://www.clinicaltrials.gov/ct2/results?term=NCT00211887&Search=Search) found that the combination of IFNβ with GA was no more effective than either therapy alone.[88] Cost-effectiveness analyses will be a factor for consideration when weighing the risks and benefits of future combination regimens.

Clinical, Imaging, and Biochemical Markers of Disease Activity. Although markers of disease activity are beyond the scope of this article, they may prove useful in predicting which patients are most likely to respond to certain medications. Individualizing treatments in this way has the potential to help avoid patients' receiving an unsuitable therapy, leading to potential cost benefits. In terms of clinical markers, current information suggests that higher EDSS or Multiple Sclerosis Functional Composite scores at baseline;[89,90] incomplete recovery from the first neurological attack;[91] shorter time to second attack;[91] sphincter, bladder, or bowel symptoms at disease onset;[91] cerebellar involvement;[91] increased relapse frequency prior to study enrollment;[91] male sex;[91] and older age[91] are all associated with increased risk of disability progression in patients with RRMS. The imaging markers—"black holes" on magnetic resonance imaging at baseline,[92] baseline or early CNS atrophy,[93,94] and baseline activity with T_2 lesions, active T_2 lesions, and/or gadolinium-enhancing[95-98] lesions—appear to be associated with disability progression. Less is known about biochemical markers. Potential biochemical marker candidates were recently reviewed in an article by Graber and Dhib-Jalbut (2011).[99] Although the potential biochemical markers cerebrospinal fluid neurofilament chains, tumor necrosis factor alpha, and the cell surface ligands Fas/FasL have been correlated with patient disability, there are currently no reliable, validated MS biomarkers available for widespread clinical use. Prospective evaluations of potential candidates are needed to confirm that biochemical markers reliably predict disability progression during MS therapy.

Conclusions: Implications for Managed Care Organizations and Payers

Retrospective claims analyses can be useful to organizations ascertaining plan-specific disease management efforts versus national and regional norms. Data from the literature and the Total Resource Utilization Benchmarks analysis suggest that DMTs account for a substantial proportion of the total costs of MS. To evaluate this possibility, a review of the literature was conducted to profile the cost-effectiveness of the approved DMTs. Findings from cost-effectiveness research indicate that there are advantages for starting DMT treatment early in the disease course. This is in line with efficacy findings from clinical trials of IFNβ formulations and GA that have shown clear benefits, measured as reported delays in patient conversion to CDMS, when these agents are administered to patients after their first neurologic episode. Therefore, in line with the recommendations of the National Clinical Advisory Board of the National MS Society (http://www.nationalmssociety.org/for-professionals/healthcare-professionals/publications/expert-opinion-papers/download.aspx?id=8), the literature suggests initiating treatment with IFNβ or GA for patients who are at high risk of MS (i.e., patients with CIS).

On the basis of the available evidence, there is little evidence to separate the effectiveness or costs of IFNβ and GA formulations, which are typically used as first-line therapies. Despite the limitations of cross-study comparisons, this review found that these agents produced generally comparable cost-effectiveness, although research to date has been conflicting. Therefore, when considering a first-line agent, current therapy decisions will most likely be made based on preference, adherence, convenience, and tolerability.

Natalizumab is clinically effective and has been shown to be potentially more cost-effective than other DMTs in certain analyses, particularly in patients with more advanced disease. However, risk-benefit considerations are warranted due to the risk of PML as a possible rare adverse event. In the United States, natalizumab is approved for use as monotherapy for the treatment of relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations in patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy, although its recommended use is not restricted to second-line therapy. With the recent development of an assay that detects antibodies against JCV, clinicians can now stratify patients who may be at higher and lower risk of developing PML based on anti-JCV antibody status, prior immunosuppressant use, and duration of natalizumab exposure.[21,24] However, the impact of this assay on the overall cost-effectiveness of natalizumab has not been established.

Finally, fingolimod has shown promising efficacy in MS and has recently gained FDA approval for treatment of patients with RRMS. However, as discussed, questions remain about the long-term safety and cost-effectiveness of this drug. Addressing these questions will facilitate a more confident placement of this agent in the treatment algorithm.

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