Quantifying the Role of Natalizumab in Health and Economic Outcomes in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system defined by inflammation, demyelination, and axonal degeneration. MS progresses slowly and usually strikes at a fairly young age, causing both the direct and indirect costs of treating the disease to be very high. The direct costs to treat MS can average up to $30,000 per year; including indirect costs raises this to as high as $47,000. Natalizumab has proven to be able to reduce the signs of MS and has been associated with improvements in health-related quality-of-life measures; these effects have the potential to also reduce some of the economic burden of this debilitating disease. The significant clinical burden of MS can be quantified by cost and societal impact, important information to both payers and employers.

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For author information and disclosures, see end of text.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammation, demyelination, and axonal degeneration. In the United States, there are an estimated 400,000 people with MS.[1] Most patients are diagnosed between the ages of 20 and 50 years, but MS can afflict both younger and older persons.[1]

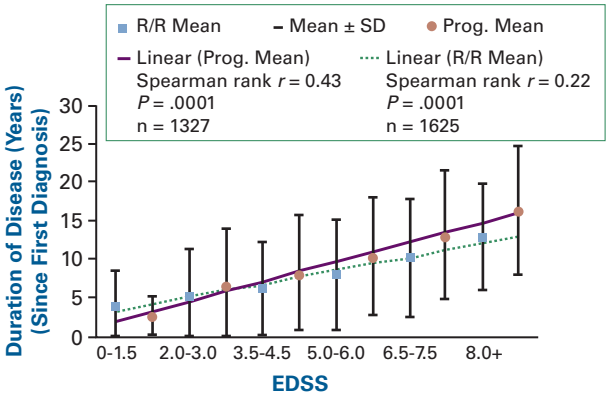
MS is a disease that afflicts many people who have their most productive years ahead. The economic burden associated with MS can be considerable, especially when taking into account both direct costs (eg, MS-specific healthcare) and indirect costs (eg, lost ability to work). The purpose of this article is to quantify the burden of MS in terms of domains that directly or indirectly affect economic outcomes, and identify the economic impact of natalizumab on those same outcomes.

The Clinical Burden of MS

MS is a progressive disease that can be disabling as early as 6 years after diagnosis, with permanent disability often occurring within 10 years after diagnosis if not properly treated.[2] Disease progression can be quantified using the Expanded Disability Status Scale (EDSS).[3] EDSS scores range from 0 to 10; a score of 0 indicates no disability, while a score of 10 indicates death due to MS. It is a nonlinear scale with emphasis on ambulation. Mild MS (ie, patients without ambulatory difficulty) is defined as an EDSS score less than 4.0, moderate MS (ie, those with some ambulation impairment) have an EDSS score between 4.0 and 6.0, and more severe MS (ie, patients with significant ambulation impairment) is defined by scores greater than 6.0. With more severe MS, mechanical assistance is utilized. The use of unilateral equipment (eg, cane, crutch, brace) begins with a score of 6.0, and wheelchair use begins with a score of 7.0. As shown in Figure 1, the level of disability in untreated MS generally increases over time.[2] On average, patients who are not receiving treatment have EDSS scores of 4.0 or higher by the 7th year after initial diagnosis.

The disabilities that patients with MS experience are numerous and are not just physical disabilities. Cognitive impairment is a major concern for MS patients. Chiaravalloti and DeLuca noted that cognitive impairment affects 43% to 70% of patients with MS.[4] Cognitive impairment in patients with MS usually relates to slowed mental processing speed and difficulty with memory recall and

Figure 1. Duration of Disease Progression



EDSS indicates Expanded Disability Status Scale.
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multitasking. Basic intelligence is usually not affected. These patients frequently cannot "keep up" with coworkers. Thus, a decline in cognitive function may be the major reason many patients with MS are unable to work. Over half of patients with MS are unemployed within 10 years of diagnosis, and this is often attributed to a decline in cognition.[4]

One of the most common physical disabilities in MS patients is overwhelming physical fatigue. Based on a Canadian study of 85 patients, a total of 40% report fatigue on a daily basis; 69% of these patients stated that fatigue was the worst, or one of the worst, symptoms of MS.[5] Other common symptoms of MS include numbness, gait disturbances, poor balance and coordination, bladder and/or bowel dysfunction, visual impairment, dizziness, vertigo, sexual dysfunction, pain, and spasticity.[6]

Overall, the decline in physical and mental function associated with MS greatly impacts quality of life. Rudick et al examined health-related quality of life (HRQOL) in patients enrolled in 2 large phase 3 clinical trials (SENTINEL [Safety and Efficacy of Natalizumab in Combination with Interferon beta-1a] and AFFIRM [Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis]). Using the Short Form-36 instrument, which is complementary to the EDSS and provides a generic (ie, not specific to MS patients) measure of HRQOL, it was observed that baseline physical and mental component summary scores were significantly lower than the general population.[7] Not surprisingly, HRQOL was directly related to the severity of MS as well as to whether the patient was experiencing a relapse (defined as a period of worsening neurologic function).

The Economic Burden of MS

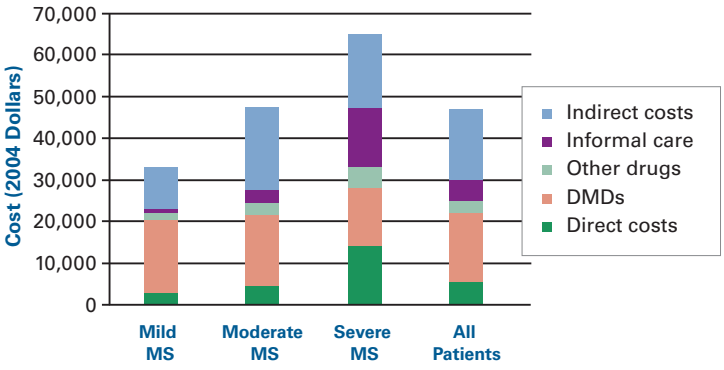
The economic burden associated with MS is daunting, and includes considerable medical and nonmedical expenditures. With regard to medical costs, a study by Kobelt et al estimated total direct medical costs of MS to be $29,634 per year (2004 dollars); total costs including indirect costs were $47,215.[8]

Another US study reported the average annual costs for the direct care of MS to be $12,879 (2004 dollars).[9] Compared with the costs reported above by Kobelt et al, there is a visible dissimilarity, which was due to methodology. The analysis by Prescott et al utilized costs for medical care taken directly from administrative claims data specific to MS (as compared with information from survey data mapped to costs used by Kobelt et al). Additionally, the patient population differed; the latter analysis represented a larger percentage of patients not currently using disease-modifying treatments (DMTs). Among patients receiving DMTs, reported costs were closer to those in the Kobelt et al study. The analysis by Prescott and colleagues also noted that MS costs were dependent on the general health of the patient; patients reporting symptoms such as gait abnormality, ataxia, convulsions, malaise/fatigue, optic neuritis, or spasms had significantly higher total costs.[9]

Generally, the cost of MS is dependent on its severity. A study based in Europe estimated the total mean annual costs per patient (2005 values) to be €18,000 ($22,500) for mild MS (EDSS score <4.0), €36,500 ($45,625) for moderate MS (EDSS score 4.0-6.5), and €62,000 ($77,500) for severe MS (EDSS score >7.0).[10] Interestingly, this study noted that direct medical costs (including pharmacy) were fairly even among the 3 categories, while indirect costs increased sharply with increased severity. A similar pattern was observed in the United States, where informal costs rose dramatically with increased severity of disease (**Figure 2**).[8] In this latter study, informal care referred to the time spent by family and friends caring for a patient with MS. A study from Germany showed a similar pattern; the average annual cost of MS to the payer was €18,988 ($23,735 [2005 dollars]) while the cost to society was €39,998 ($49,998).[11] A large portion of the societal costs were informal care and loss of productivity/early retirement. The authors of this study also noted that as MS progresses, patients must purchase walking aids and wheelchairs, modify cars/houses for handicap access, and rely on family and friends for some form of help. They calculated that if a patient with MS requires approximately 500 hours of assistance per year, this results in an additional cost of €4400 ($5500) per patient.[11] A recent presentation by Miltenburger and Gunther also showed that the cost of informal care for patients with MS was much higher as the disease progressed.[12] In Germany, 70% of informal care

costs were allocated for patients with EDSS scores greater than 7. In Italy, 82% of early retirement costs and 92% of informal care costs were related to caring for patients with EDSS scores greater than 5.0.

Figure 2. Cost Distribution for Managing Patients With MS



DMD indicates disease-modifying drugs; MS, multiple sclerosis.
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Impact of Natalizumab on Clinical Outcomes

The introduction of natalizumab in 2006 gave clinicians a new treatment option for relapsing MS. The landmark AFFIRM study showed that natalizumab reduced the risk of sustained progression of disability over 2 years by 42% (hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.43-0.77; P <.001); reduced the rate of clinical relapse at 1 year by 68% (0.23 vs 0.73, respectively; P <.001), which was maintained at 2 years; and reduced the accumulation of new or enlarging T2 hyperintense lesions by 83% (mean number of lesions, 1.9 with natalizumab and 11.0 with placebo; P <.001), as detected by magnetic resonance imaging.[13]

In addition to these clinical outcome improvements, natalizumab was also shown to improve quality-of-life measures in patients with MS. For example, Rajagopalan et al measured MS-specific quality-of-life measures using the Multiple Sclerosis Impact Scale-29 in patients receiving natalizumab (n = 296) over the course of 6 infusions and found that patients had significant improvements in both physical and psychological scores (physical impact score: baseline 48 ± 23, third infusion 40 ± 23, sixth infusion 40 ± 25 [P <.0001]; psychological impact score: baseline 41 ± 22, third infusion 33 ± 21, sixth infusion 33 ± 23 [P <.0001]).[14] Similarly, a small study reported improvements with natalizumab in self-reported fatigue, cognition, and weakness in 70% (41/59), 68% (40/59), and 68% (40/59) of patients, respectively.[15]

Natalizumab treatment has similarly been associated with improvements in cognition. Preliminary results from an ongoing study were recently presented by Stephenson et al.[16] Among 186 patients with MS enrolled in the TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing Program, natalizumab was associated with a significant improvement in cognitive function, as measured by the 6-question Medical Outcomes Study Cognitive Functioning scale (baseline score 24.63 ± 8.50; third infusion score 27.04 ± 7.06 [P <.001]). Also, after only 3 months of treatment, natalizumab was associated with significantly less fatigue as measured by the Modified Fatigue Impact Scale (baseline score 12.72 ± 4.35; third infusion score 10.38 ± 4.83 [P <.001]). Other studies have reported reductions in fatigue following natalizumab treatment.[17]

The Multiple Sclerosis Functional Composite (MSFC) score is a brief measure of functional capacity that examines ambulation, upper extremity function, and cognitive function with one validated test of each function. In the phase 3 AFFIRM study, natalizumab was associated with a 33% relative reduction in the cumulative probability of MSFC Progression-20 (defined as worsening from baseline on scores for at least 1 MSFC component by 20%) (HR, 0.67; 95% CI, 0.52-0.86; P = .002).[18] The improvement in MSFC scores in this study was driven primarily by improved function in cognition and upper extremity assessments.

Overall, natalizumab has been associated with improvements in various aspects of quality of life by providing physical, cognitive, and psychological benefits in patients with MS. How these improvements lead to lower direct or indirect medical costs is only now being studied.

Impact of Natalizumab on Economic Outcomes

Economic Models

To date, available economic studies on natalizumab are limited to mostly budget impact models that quantify the cost of a drug for managed care payers. Chiao and Meyer developed both a cost-effectiveness and budget impact model to address the cost-effectiveness of natalizumab versus other DMTs and the impact of natalizumab on US payers.[19] In their model, a hypothetical plan population of 1 million members was used, with an estimated 592 of those members having relapsing MS requiring natalizumab or another DMT.[19] The model inputs were drug acquisition costs (wholesale acquisition costs), costs of drug administration and monitoring, costs of treating relapses, anticipated reduction in relapse rates after 2 years of therapy, and estimated market utilization of natalizumab. Outcomes included total 2-year costs of therapy per patient,

Table 1. Relative Reduction on Relapse Rates Used for Budget Impact Model by Chiao and Meyer[21]

Disease-Modifying Therapy	No. Relapses (Placebo)	No. Patients (Placebo)	2-Year Relative Relapse Rate Reduction, %	No. Relapses Avoided per Patient[a]	No. Relapses per Patient[b]
Natalizumab[c]	1.47	315	67[d]	1.27	0.63
Intramuscular IFN beta-1a[e]	1.64	143	32	0.61	1.29
IFN beta-1b[f]	2.54	123	34	0.65	1.26
Glatiramer acetate[g]	1.68	126	29	0.55	1.35
Subcutaneous IFN beta-1a[h]	2.56	187	32	0.61	1.29

IFN indicates interferon.
[a]The number of relapses avoided per patient was calculated as the weighted average number of relapses per patient before treatment multiplied by the 2-year relative relapse reduction for each therapy.
[b]The number of relapses per patient was calculated as the weighted average number of relapses per patient before treatment minus the number of relapses avoided per patient.
[c]Polman CH, O'Connor PW, Havrdova E, et al. *N Engl J Med.* 2006;354(9):899-910.
[d]This relative reduction was based on an analysis presented in the natalizumab prescribing information on the intention to treat population, using mean per patient relapse rate. Polman et al[c] describe a relative reduction of 68% for natalizumab based on a predefined analysis using group mean data.
[e]Jacobs LD, Cookfair DL, Rudick RA, et al; Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol.* 1996;39(3):285-294.
[f]The IFNB Multiple Sclerosis Study Group. *Neurology.* 1993;43(4):655-661.
[g]Johnson KP, Brooks BR, Cohen JA, et al; Copolymer Multiple Sclerosis Study Group. *Neurology.* 1995;45(7):1268-1276.
[h]PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet.* 1998;352(9139):1498-1504.

costs per relapse avoided for each treatment, and overall 2-year costs to the health plan and per-member per-month costs (all costs adjusted to 2008 dollar amounts). The results of this study were very interesting. The 2-year cost of therapy was highest for natalizumab (natalizumab, $72,120; intramuscular [IM] interferon [IFN] beta-1a, $56,790; IFN beta-1b, $56,773; subcutaneous [SC] IFN beta-1a, $58,538; and glatiramer acetate [GA], $57,180). However, the cost per relapse avoided was dramatically lower for natalizumab compared with the other DMTs (natalizumab, $56,594; IFN beta-1b, $87,791; IM IFN beta-1a, $93,306; SC IFN beta-1a, $96,178; and GA, $103,665) because natalizumab was associated with half as many relapses as the other treatments (Table 1).[19]

Table 2. Natalizumab Economic Study: Patient Characteristics

N	349
Average age[a]	44.8
Age distribution, y, N (%)	
18-25	16 (4.6)
26-39	89 (25.5)
40-64	233 (66.8)
65+	11 (3.2)
Sex, N (%)	
Female	261 (74.8)
Male	88 (25.2)

[a]Age distribution presented as of 2007, when natalizumab therapy was initiated.

Kobelt et al used a Markov model to compare drug efficacy and costs with natalizumab and other DMTs.[20] Data from the AFFIRM study (n = 942) and the Stockholm MS registry (n = 512) were assessed. Total costs (2005 values) over a 20-year period were similar in the 2 groups (natalizumab, €609,850 [or $762,313]; other DMTs, €613,680 [or $767,100]).[20] The study also determined that when only direct healthcare costs were included, the cost per quality-adjusted life-year (QALY) gained with natalizumab was €38,145 ($47,682).[21]

A British cost-effectiveness analysis examined the pharmacoeconomics of natalizumab versus standard DMT therapy in patients with highly active relapsing-remitting MS. At a willingness-to-pay threshold of £30,000 ($37,500) per QALY, the probability of natalizumab being cost-effective from a societal perspective compared with other agents was greater than 89%.[21] This model included indirect costs to society, such as loss of productivity, which is common in patients with highly active relapsing-remitting MS. Therefore, the model may be closer to real-world observations, as patients and society make numerous financial adjustments as the symptoms of MS progress.

Finally, a US economic model study compared natalizumab with GA and took into account medical costs, nonmedical costs (eg, devices and investments to adapt living conditions), and informal care by family and friends.[22] The model predicted that the incremental cost per QALY for natalizumab was $606,228 (2007 dollars) (vs $496,222 for patients receiving GA).[22] The 10- to 20-fold increase in financial burden calculated in this model (compared with the

Table 3. Natalizumab Economic Study: Pharmacotherapy by Year

	Year		
	2006	2007	2008
Drug/Drug Class	N (%)	N (%)	N (%)
Self-injectable DMTs	265 (75.9)	192 (55.0)	18 (5.2)
Beta IFNs	199 (57.0)	131 (37.5)	9 (2.6)
IFN beta-1a (IM)	92 (26.4)	57 (16.3)	1 (0.3)
IFN beta-1a (SC)	82 (23.5)	56 (16.0)	6 (1.7)
IFN beta-1b	34 (9.7)	18 (5.2)	2 (0.6)
Glatiramer acetate	88 (25.2)	65 (18.6)	10 (2.9)
Infused DMTs	13 (3.7)	349 (100.0)	349 (100.0)
Natalizumab	0 (0.0)	349 (100.0)	349 (100.0)
Mitoxantrone	13 (3.7)	5 (1.4)	2 (0.6)
Anticonvulsants	123 (35.2)	132 (37.8)	121 (34.7)
Antidepressants	197 (56.4)	201 (57.6)	195 (55.9)
Antidiarrheals	4 (1.1)	6 (1.7)	4 (1.1)
Antihistamines	6 (1.7)	8 (2.3)	2 (0.6)
Antispastics	146 (41.8)	145 (41.5)	113 (32.4)
Benzodiazepines	99 (28.4)	86 (24.6)	70 (20.1)
Cognition agents	9 (2.6)	11 (3.2)	13 (3.7)
Corticosteroids	183 (52.4)	172 (49.3)	125 (35.8)
Migraine agents	22 (6.3)	30 (8.6)	29 (8.3)
Narcolepsy agents	69 (19.8)	76 (21.8)	70 (20.1)
Narcotic analgesics	138 (39.5)	136 (39.0)	143 (41.0)
NSAIDs	65 (18.6)	69 (19.8)	72 (20.6)
Overactive bladder agents	82 (23.5)	95 (27.2)	90 (25.8)
Parkinson's agents	41 (11.7)	39 (11.2)	38 (10.9)
Stimulants	21 (6.0)	26 (7.4)	24 (6.9)

DMTs indicates disease-modifying therapies; IFN, interferon; IM, intramuscular; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous.

above studies) was attributed to differences in utilities used for QALY calculations. This latter study illustrates the strong need to clarify the cost of care for MS patients and the need for additional real-world data.

Real-World Observational Data[23]

In addition to the above budget models, real-world observational data are available on the financial impact of natalizumab. Below is a summary of recent retrospective medical and pharmacy claims data obtained from a large US-based database. This study did not consider nonmedical costs associated with MS but does provide an excellent assessment of cost to the payer.

Methods

Data were obtained from the IMS/PharMetrics Integrated Patient-Centric Database, which contains medical and pharmaceutical claims for more than 55 million unique patients from 75 health plans across the United States. This database includes both inpatient and outpatient diagnoses (in *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] format) and procedures (in *ICD-9-CM*, *Current Procedural Terminology*, and Health Care Financing Administration Common Procedure Coding System formats), as well as community and mail-order pharmacy claims; available data for pharmacy claims are based primarily on National Drug Code and Common Procedure Coding System drug codes. Only health plans submitting data for all of their members are included in the database. Data submissions were subjected to a series of data quality checks to ensure a standardized format and minimize error rates. Only patients diagnosed with MS and who started

Table 4. Natalizumab Economic Study: Economics by Year

	Year		
	2006	2007	2008
Service Category	**Average Annual Utilization[a]**		
Inpatient	2.54	2.39	2.11
Outpatient	24.40	37.14	37.61
Emergency department	0.94	0.83	0.78
Pharmacy	13.99	20.19	22.58
	Average Annual Costs, $		
Inpatient	3014	2682	1841
Outpatient	6919	11,629	10,619
Emergency department	577	335	257
Pharmacy	13,699	30,048	44,971
Total Charges	**24,209**	**44,694**	**57,689**

[a]Reflects number of services received during the study year.

natalizumab during 2006 or 2007 and continued therapy through 2008 were included in this analysis. All studied patients had 3 full years of eligibility and contribution of claims data. Charges and utilization of medical services and prescription drugs were identified and captured using the Episode Treatment Groups software.

Results

As shown in Table 2, the mean age of patients was 44 years and the majority was female. Table 3 shows changes in pharmacotherapy over the 3-year period. The percentage of patients requiring medications for relief of MS-related symptoms (eg, corticosteroids, benzodiazepines, antispastics) decreased from 2007 to 2008. A total of 45% of patients maintained sole use of natalizumab in 2007 (ie, no other DMTs); by 2008, that percentage increased to 94% (data not shown).

Total expenditures are shown in Table 4. In 2008, the year in which natalizumab was the sole DMT for most patients, outpatient costs decreased, as did the number of emergency department visits and hospitalizations due to MS. Offsetting this, pharmacy expenditures increased.

Conclusions

While the time frame used in this study limits definitive conclusions, it does provide a unique opportunity to examine changes in expenditures when patients switch medications. Interestingly, the switch to natalizumab was associated with a decrease in costly emergency department visits and hospitalizations. This pattern was observed in a previous study using 2005/2006 data for other DMTs in which pharmacy costs rose while inpatient and outpatient costs declined.[24] Patients appropriate for treatment with natalizumab, however, generally have greater disease severity. In this study, the severity of MS was not provided. Future studies that detail MS severity as well as the economic and physical changes that result from long-term natalizumab therapy are warranted.

Summary

MS poses a significant clinical and financial burden to patients, payers, health systems, and society. As the clinical manifestations of MS progress, the economic and societal burdens also increase. Natalizumab therapy can reduce MS signs, and preliminary economic studies indicate that natalizumab may reduce medical costs as well. While natalizumab itself represents a significant expenditure, the associated reduction in relapse rates and disease progression may reduce overall costs. Additional long-term studies are needed to better quantify the medical and nonmedical costs of natalizumab therapy.

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