The cost of multiple sclerosis drugs in the US and the pharmaceutical industry

Too big to fail?

OPEN

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ABSTRACT

Objective: To examine the pricing trajectories in the United States of disease-modifying therapies (DMT) for multiple sclerosis (MS) over the last 20 years and assess the influences on rising prices.

Methods: We estimated the trend in annual drug costs for 9 DMTs using published drug pricing data from 1993 to 2013. We compared changes in DMT costs to general and prescription drug inflation during the same period. We also compared the cost trajectories for first-generation MS DMTs interferon (IFN)-β-1b, IFN-β-1a IM, and glatiramer acetate with contemporaneously approved biologic tumor necrosis factor (TNF) inhibitors.

Results: First-generation DMTs, originally costing $8,000 to $11,000, now cost about $60,000 per year. Costs for these agents have increased annually at rates 5 to 7 times higher than prescription drug inflation. Newer DMTs commonly entered the market with a cost 25%–60% higher than existing DMTs. Significant increases in the cost trajectory of the first-generation DMTs occurred following the Food and Drug Administration approvals of IFN-β-1a SC (2002) and natalizumab (reintroduced 2006) and remained high following introduction of fingolimod (2010). Similar changes did not occur with TNF inhibitor biologics during these time intervals. DMT costs in the United States currently are 2 to 3 times higher than in other comparable countries.

Conclusions: MS DMT costs have accelerated at rates well beyond inflation and substantially above rates observed for drugs in a similar biologic class. There is an urgent need for clinicians, payers, and manufacturers in the United States to confront the soaring costs of DMTs. *Neurology*® 2015;84:2185–2192

GLOSSARY

AWP = average wholesale price; **DMT** = disease-modifying therapy; **FDA** = Food and Drug Administration; **IFN** = interferon; **MS** = multiple sclerosis; **QALY** = quality-adjusted life-year; **TNF** = tumor necrosis factor; **VA** = Veterans Affairs; **WAC** = wholesale acquisition cost.

The landscape of multiple sclerosis (MS) treatment has changed dramatically over the last decade. As of November 2014, 12 disease-modifying therapies (DMTs) for MS have been approved by the US Food and Drug Administration (FDA). Despite the availability of more treatment options, costs for all MS DMTs have increased sharply. Between 2008 and 2012, US DMTs sales doubled from $4 billion to nearly $9 billion annually.[1] In 2004, the average annual DMT cost per person was $16,050, accounting for half of all direct medical costs for patients with MS.[2] Currently, the average annual cost for interferon (IFN)–β-1b (Betaseron; Bayer HealthCare Pharmaceuticals, Whippany, NJ) is over $60,000.[3] Although high drug costs are a hallmark of specialty pharmaceutical classes, such as DMTs, the unexplained escalation in costs for older, first-generation MS therapies such as IFN-β-1b, IFN-β-1a IM (Avonex; Biogen Idec, Cambridge, MA), and glatiramer acetate (Copaxone; Teva Pharmaceuticals, North Wales, PA) has caused concern in the neurology community.[4,5]

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Results: First-generation DMTs, originally costing $8,000 to $11,000, now cost about $60,000 per year. Costs for these agents have increased annually at rates 5 to 7 times higher than prescription drug inflation. Newer DMTs commonly entered the market with a cost 25%–60% higher than existing DMTs. Significant increases in the cost trajectory of the first-generation DMTs occurred following the Food and Drug Administration approvals of IFN-β-1a SC (2002) and natalizumab (reintroduced 2006) and remained high following introduction of fingolimod (2010). Similar changes did not occur with TNF inhibitor biologics during these time intervals. DMT costs in the United States currently are 2 to 3 times higher than in other comparable countries.

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DMTs and the trend in costs for older DMTs, and (3) compare DMT costs in the United States to those in other countries. This study suggests the need for the neurology community to advocate for changes in the pricing of MS treatments.

METHODS Although the FDA had approved 12 DMTs for MS as of November 2014, we did not include 3 in our analysis. Cost data were not available at the time of our analysis for the 2 most recently approved DMTs: peginterferon-β-1a (Plegridy; Biogen Idec) and alemtuzumab (Lemtrada; Genzyme, Cambridge, MA). Mitoxantrone (generic, multiple manufacturers), approved in 2000 for MS, was excluded because it is much less commonly used to treat MS due to safety concerns.[6,7] For the remaining 9 FDA-approved drugs, we computed the average annual acquisition costs for each month from July 1993 (approval date for IFN-β-1b) through December 2013. We estimated acquisition costs using average wholesale price (AWP) published by First DataBank.[3] Although most third-party payers have moved away from AWP-based reimbursement formulas, it was the prevailing methodology for most of the study period and provides a consistent measure of price for comparisons of change over the past 20 years.[8] AWP reporting was phased out in 2011 and acquisition costs were then estimated using wholesale acquisition cost (WAC) with the conversion AWP = 1.2 × WAC.[8] We applied a 12% discount to AWP, the median discount that state Medicaid programs reimburse pharmacies, to estimate the amount paid to pharmacies by third-party payers.[9] We then computed the effective percentage increase in annual costs and compared this to changes in the consumer price index for prescription drugs and all consumer goods and services (general inflation) over the same period using data from the US Bureau of Labor Statistics.[10]

Next, we compared the median annual cost trends for first-generation MS DMTs IFN-β-1b, IFN-β-1a IM, and glatiramer acetate to the contemporaneously approved biologic tumor necrosis factor (TNF) inhibitors etanercept (Enbrel; Amgen, Thousand Oaks, CA) and adalimumab (Humira; AbbVie, North Chicago, IL) using segmented regression analyses.[11] We computed annual costs for TNF inhibitors using the same approach described for the MS drugs based on FDA-approved doses for rheumatoid arthritis. Annual costs were estimated quarterly beginning the fourth quarter of 1998 (the quarter etanercept was approved) until the fourth quarter of 2013 (61 total quarters). Four major periods of change were examined: (1) a baseline period preceding the approval of IFN-β-1a SC (Rebif; EMD Serono, Rockland, MA) (fourth quarter 1998 to first quarter 2002); (2) a period from the approval of IFN-β-1a SC to the re-introduction of natalizumab (Tysabri; Biogen Idec) (second quarter 2002 to second quarter 2006); (3) a period from the re-introduction of natalizumab to the approval of fingolimod (Gilenya; Novartis Pharmaceuticals, East Hanover, NJ) (third quarter 2006 to third quarter 2010); and (4) a period following the approval of fingolimod (fourth quarter 2010 to fourth quarter 2013). We selected the re-introduction date for natalizumab (June 2006–second quarter 2006) because it was only available for 2 months before marketing was suspended in 2005 to evaluate the risks of progressive multifocal leukoencephalopathy.

The general form of the segmented regression model (without interaction parameterization) was $\log(Y_t) = \beta_0 + \beta_1 \times \text{Time}_t + \beta_2 \times \text{Rebif}_t + \beta_3 \times \text{Time Rebif}_t + \beta_4 \times \text{Tysabri}_t + \beta_5 \times \text{Time Tysabri}_t + \beta_6 \times \text{Gilenya}_t + \beta_7 \times \text{Time Gilenya}_t + \beta_8 \times \text{DrugType} + e_t$. We log-transformed the dependent variable annual cost because initial plots of quarterly data were nonlinear. Because of this, the estimated β-coefficients are interpreted as a percent change.[12] For each period, we report the quarterly percentage change (trend) in median costs for DMTs and TNF inhibitors individually and relative to each other. Statistical analyses were performed using PROC AUTOREG in SAS version 9.2 (SAS Institute, Cary, NC).

Finally, we compared the most recent annual cost of therapy for each DMT to US dollar-adjusted costs from the United Kingdom, Canada, and Australia, a convenience sample of developed countries with accessible cost data. The following conversion rates (as of April 2, 2014) for cost data were applied: Canada (0.91), United Kingdom (1.66), Australia (0.92). In the United Kingdom, the National Health Service publishes net prices in the British National Formulary.[13] Canadian drug costs were estimated using drug benefit prices published through Ontario's Exceptional Access Program, although costs can vary by province.[14] Drug costs in Australia are listed in an online compendium of the Australian Pharmaceutical Benefit Scheme and represent agreed-upon prices paid by the Commonwealth of Australia.[15] We also examined costs paid by the US Department of Veterans Affairs (VA) because of their ability to negotiate discounts directly with manufacturers.[16] VA costs were estimated using Big Four pricing (or Federal Supply Schedule price if no Big Four price was listed) available through the online VA National Formulary.[16] For comparative purposes, we further adjusted US costs to account for federally mandated rebates paid to the Medicaid program.[17,18] Appendix e-1 on the *Neurology*® Web site at Neurology.org contains details of our cost and statistical modeling methods.

RESULTS First-generation DMTs IFN-β-1b, IFN-β-1a IM, and glatiramer acetate were introduced with annual acquisition costs between $8,292 and $11,532 (table 1). Over subsequent decades, costs for these DMTs rose on average 21%–36% annually. Costs of the most recently approved oral agents fingolimod, teriflunomide (Aubagio; Genzyme), and dimethyl fumarate (Tecfidera; Biogen Idec) have increased 8%–17% annually since their approval. In contrast, general and prescription drug inflation only increased 3%–5% per year during the same period. The acquisition cost of IFN-β-1b, the oldest DMT on the market, is now $61,529 a year, roughly 6 times its original cost. The cost trajectories for IFN-β-1a IM and glatiramer acetate were similar. Without accounting for any potential manufacturer rebates, there are currently no MS DMTs with an annual cost less than $50,000 per year.

The dramatic increase in costs of the first-generation DMTs was not uniform over the last 20 years. Costs for first-generation DMTs increased modestly between 1993 and 2001 (figure 1). IFN-β-1a SC, a recombinant IFN-β similar to IFN-β-1b and IFN-β-1a IM, entered the market in March 2002 with an annual cost of $15,262, 30%–60% higher than the 3 other available DMTs. The annual cost of natalizumab, the first monoclonal antibody for MS, at initial release (November 2004) was $25,850, over 50% higher than IFN-β-1b, IFN-β-1a IM, and glatiramer

Table 1 Initial (market release date) and current annual costs (December 2013) of multiple sclerosis disease-modifying therapies in the United States relative to consumer price index changes during the same period

	US approval date	Approval date, annual cost	2013 annual cost	Annualized change, %	Annualized change in CPI prescription drugs, %	Annualized change in CPI all goods and services, %
Interferon-β-1b[a] (Betaseron)	7/23/1993	$11,532	$61,529	21.0	4.8	3.0
Interferon-β-1a IM (Avonex)	5/17/1996	$8,723	$62,394	34.6	4.7	2.8
Glatiramer acetate (Copaxone)	12/20/1996	$8,292	$59,158	35.7	4.7	2.8
Interferon-β-1a SC (Rebif)	3/7/2002	$15,262	$66,394	28.1	3.6	2.7
Natalizumab (Tysabri)[b]	11/23/2004[b]	$25,850	$64,233	16.2	3.3	2.4
Interferon-β-1b[a] (Extavia)	8/14/2009	$32,826	$51,427	13.0	2.9	2.0
Fingolimod (Gilenya)	9/21/2010	$50,775	$63,806	7.9	2.4	2.2
Teriflunomide (Aubagio)	9/12/2012	$47,651	$57,553	16.8	0.0	1.1
Dimethyl fumarate (Tecfidera)	3/27/2013	$57,816	$63,315	13.8	1.0	1.3

Abbreviation: CPI = consumer price index.
CPI data source: http://www.bls.gov/cpi/data.htm.
[a] Interferon-β-1b is marketed as both Betaseron (Bayer) and Extavia (Novartis).
[b] Natalizumab was withdrawn from the market in February 2005 to evaluate progressive multifocal leukoencephalopathy risk and was reintroduced in June 2006.

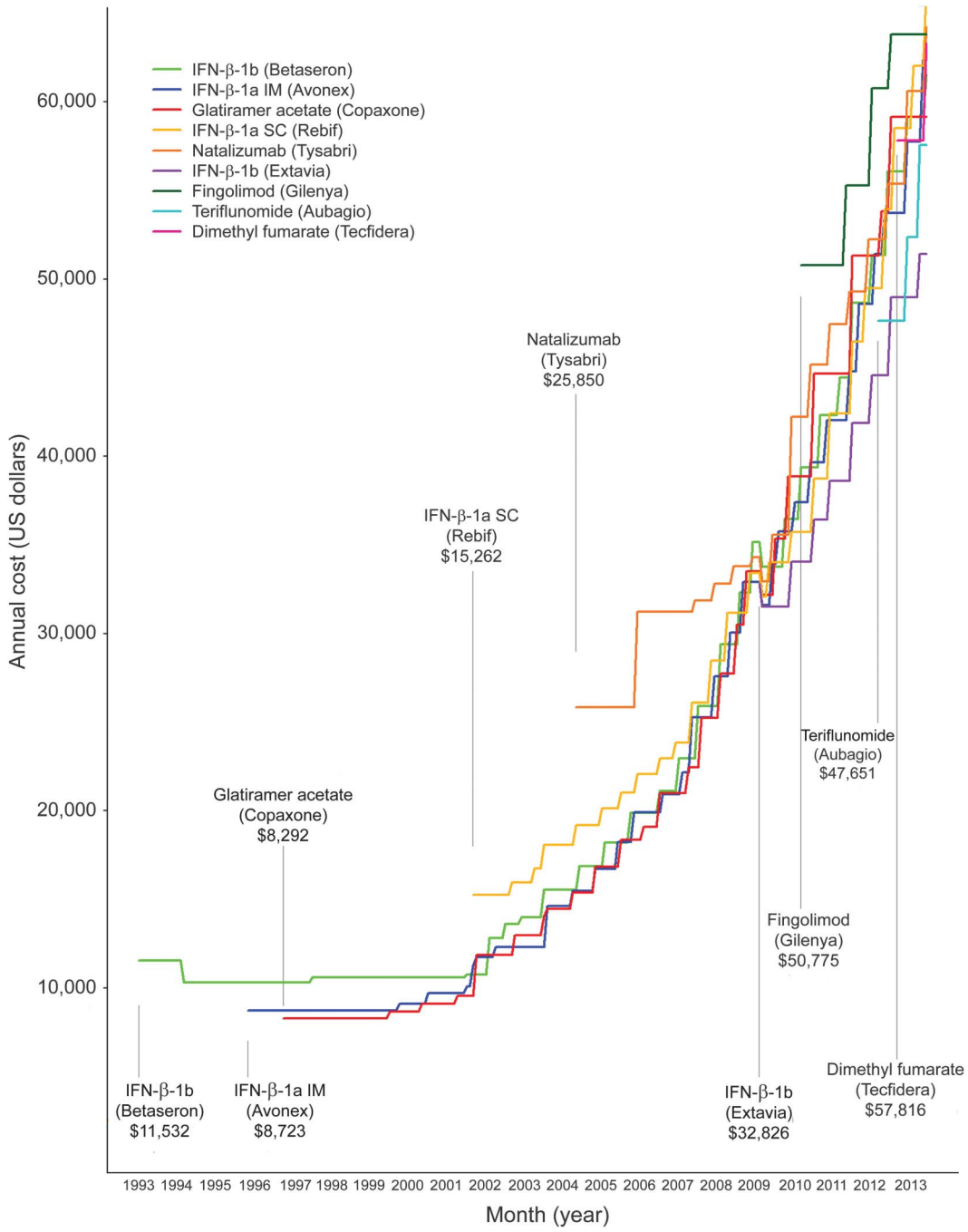
acetate. Similarly, fingolimod entered the market in 2010 with an annual cost of $50,775, over 25% higher than IFN-β-1b, IFN-β-1a IM, and glatiramer acetate.

We sought to determine whether the introduction of new MS DMTs influenced the rate of increase in cost for the first-generation DMTs and, as a comparison, used changes in the cost of TNF inhibitors (figure 2). During the baseline period of 1998–2001, costs for DMTs and TNF inhibitors increased significantly by 1.4% ($p < 0.0001$) and 2.2% ($p < 0.0001$) per quarter, respectively. During this period, the quarterly rate of increase was significantly higher for the TNF inhibitors ($p = 0.0001$). Following the introduction of IFN-β-1a SC, the trend in costs for first-generation DMTs increased significantly to 3.3% per quarter ($p < 0.0001$ for change in trend). In contrast, the rate of growth for the TNF inhibitors decreased significantly to 1.3% per quarter ($p = 0.0001$ for change in trend) and was statistically lower than the DMT trend change ($p < 0.0001$ for change in trend interaction). The re-introduction of natalizumab in 2006 was followed by another significant increase in the trend of first-generation DMT costs to 4.6% per quarter ($p < 0.0001$ for change in trend). During the same period, there was no significant change in the trend for the TNF inhibitors and the difference between the 2 classes was statistically significant ($p < 0.0001$ for change in trend interaction). Fingolimod was approved in the third quarter of 2010. Although growth in first-generation DMT costs moderated to 3.7% per quarter, it remained significantly above the quarterly growth rate for the TNF inhibitors trend, which increased to 3.1% per quarter ($p = 0.0183$ for period trend interaction).

After accounting for federally mandated Medicaid rebates, annual costs for DMTs in the United States ranged from $41,078 for IFN-β-1b (Extavia; Novartis Pharmaceuticals) to $53,032 for IFN-β-1a SC. Annual DMT costs were often more than 70% lower in the 3 comparator countries (table 2). Costs for the VA were, on average, 36% less than those paid by Medicaid, but ranged from a nearly 80% discount for IFN-β-1b to a 19% discount for fingolimod.

DISCUSSION This study documents the alarming rise in costs for MS DMTs in the United States since 2002. While we would expect that legitimate advances, such as the development of oral DMTs, might garner higher prices, the escalation in costs for first-generation agents that have been available for up to 2 decades is puzzling. Our analyses show that cost increases for IFN-β-1b, IFN-β-1a IM, and glatiramer acetate were many times higher than prescription drug inflation. First-generation MS DMT costs substantially outpaced those for a contemporaneous class of TNF inhibitor biologic agents, accelerating upwards following introduction of each new MS DMT. These results suggest that the dramatic increases in the costs of the first-generation DMTs may have been a response to the introduction of competing treatments with higher prices. The reasons for this are unclear. Classic economic theory asserts that competition should reduce or stabilize costs for the consumer as more products enter the market. However, our data suggest prices of existing DMTs paradoxically rise, quickly matching prices set by the newest competitor. Costs of MS DMTs are substantially

Figure 1 Estimated annual costs of multiple sclerosis disease-modifying therapies in the United States from 1993 to 2013



Annual costs estimated from average wholesale prices (AWP), or wholesale acquisition costs if AWP not reported, and discounted 12%. IFN = interferon.

higher in the US market than in the other countries we highlight, suggesting the dramatic increases in costs in the United States are not demanded by increases in manufacturing costs or other changes out of the control of the pharmaceutical industry.

Why the costs of MS DMTs in the United States have risen so dramatically is uncertain. However, the simplest explanation is that pharmaceutical companies raise prices of new and old MS DMTs in the United States to increase profits and our health care system puts no limits on these increases. Unlike most industrialized countries, the United States lacks a national health care system to negotiate prices directly with the pharmaceutical industry. The US Medicare program, the largest single-payer health care system in the United States, is legally prohibited from negotiating drug prices directly with the pharmaceutical industry.[19] Pharmaceutical pricing and purchasing is

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