ABSTRACT

OBJECTIVE: To examine the outcomes of use of glatiramer acetate (GA) versus beta interferons-1a (intramuscular) (1A) and -1b (1B) in patients with multiple sclerosis (MS) in a managed care setting.

METHODS: Data were obtained from a national retrospective claims database from January 1996 to June 2001. Patients were followed from the first prescription for immunomodulatory therapy until plan disenrollment or end of study time frame. The incidence of all relapses (defined as hospitalization for MS or ambulatory visit followed by use of systemic corticosteroids) as well as utilization and costs of MS-related care were examined for each group. Data were adjusted for variable follow-up using survival techniques.

RESULTS: A total of 8,457 patients receiving immunomodulatory therapy were included in the study cohort; follow-up averaged 17.3 months. Three quarters of patients were female; the mean age was 42.2 years. The risk of relapse (defined as number of new cases) at one year was significantly increased for the beta interferons relative to GA (hazard ratios: 1.15 and 1.51 for 1A and 1B, respectively, P<0.01). Mean (±SD) costs of care also were reduced among GA patients ($9,522 ±$9,706 versus $9,957 ±$9,526 for 1A and 1B, respectively). These findings persisted in multivariate analyses, controlling for differences in demographic characteristics and propensity scores for immunomodulatory therapy.

CONCLUSIONS: Glatiramer acetate is associated with reductions in the incidence of relapse and costs of care relative to the beta interferons among this large group of managed care patients with MS.

KEYWORDS: Multiple sclerosis, Immunomodulatory therapy, Costs and costs analysis, Relapse rates

J Managed Care Pharm. 2002(8):6:469-76

Authors

DANIEL A. OLLENDORF, MPH, is Director, Analytic and Consulting Services, and EVGUENIA JILINSKAIA, PhD, is Senior Biostatistician at PharMetrics, Inc., Watertown, Massachusetts; MERRIKAY OLEEN-BURKEY, PhD, is Director, Health Outcomes Research at Teva Neuroscience, Inc., Kansas City, Missouri.

CORRESPONDING AUTHOR: Daniel A. Ollendorf, Director, Analytic and Consulting Services PharMetrics, Inc., 150 Coolidge Avenue, Watertown, MA 02472 Tel: (617) 972-8590; Fax: (617) 972-8587; E-mail: dollendorf@pharmetrics.com

Copyright© 2002, Academy of Managed Care Pharmacy. All rights reserved.

M ultiple sclerosis (MS) is a costly and debilitating disease. Approximately 350,000 persons in the United States are currently diagnosed with MS; it is the most common cause of chronic neurologic disability in young adults. While the clinical course of MS varies substantially by patient, the disease typically progresses to some level of disability in approximately two thirds of MS patients. Regardless of the level of disability, patients with MS often report negative psychological and social impacts from the disease. The direct medical costs of MS also are substantial. Total annual expenditures for medical services per MS patient have been reported to range from $7,000 to $13,000 in this country, reflecting levels 2 to 3 times higher than those for all private and public insurance enrollees.

Historically, pharmacologic treatment of MS has revolved around amelioration of symptoms (e.g., use of benzodiazepines and muscle relaxants to control spasticity and use of corticosteroids to reduce the severity of MS relapses). Recently, however, the introduction of several new medications has changed MS management. These medications, which include glatiramer acetate (GA) (Copaxone, Teva Pharmaceutical Industries, Ltd.), a synthetic, noninterferon polypeptide of 4 amino acids, as well as the type 1 beta interferons (i.e., beta interferon-1a (1A) [Avonex, Biogen Inc.] and beta interferon-1b (1B) [Betaseron, Berlex Laboratories, Inc.]) have been demonstrated to be effective in reducing the rate of relapse as well as slowing disease progression in the “relapsing-remitting” form of MS. At the time this project was completed, the newest beta interferon 1a (Rebif, Serono S.A.) was not commercially available in the United States.

The precise action of beta interferons in MS is unknown. However, these drugs are known to decrease lymphocyte proliferation and interferon gamma expression, induce anti-inflammatory Th2 cytokines, and most importantly to the anti-inflammatory effect, diminish the migration of activated T cells across the blood-brain barrier. In contrast, the observed effects of glatiramer acetate are quite distinct from those of the beta interferon and include (a) competition with myelin-basic protein (MBP) for binding to the major histocompatibility complex (MHC) molecules; (b) competition of bound glatiramer acetate and MHC with MBP/MHC for binding to the T-cell receptor; (c) induction of compound-specific Th2 cells, leading to a profound Th2 shift; and (d) migration of compound-specific cells into the central nervous system. A fifth mechanism, that of a neuroprotective role, has also been observed in relation to optic nerve damage.
In addition to these mechanistic differences, data from clinical trials and postmarketing surveillance studies suggest that glatiramer acetate may have several distinct advantages relative to the interferons, including a relatively mild side-effect profile allowing for less use of concomitant medications such as acetaminophen and NSAIDs, lack of neutralizing antibodies, and reduced need for laboratory monitoring. These advantages may be associated with greater durability of treatment, better outcomes, and reduced utilization and costs relative to interferon therapy. Patterns of pharmacotherapy as well as the costs and effects of these 3 medications have never been compared under conditions of typical clinical practice, however. To address these needs, an examination of the impact of GA on the utilization and costs of MS-related care relative to that of beta interferon therapy was undertaken, using data from a proprietary database.

Methods

Overview

Data for this study were obtained on all patients with one or more institutional or provider claims with a listed diagnosis of MS (ICD-9-CM 340) who were in the database between January 1, 1996, and June 30, 2001. Patients were then classified into 3 treatment groups based on data on the first paid pharmacy claim observed during the study period (i.e., GA, 1A, or 1B). Each patient was assigned an “index date” based on the date of the first prescription for immunomodulatory therapy.

A variety of measures were then compared during the “follow-up period” (i.e., beginning with the index date) between patients in the 3 treatment groups, including the cumulative incidence of relapses, time to first relapse, and the mean number of relapses, as well as the utilization and costs of selected MS-related medications and health care services. Because the duration of eligibility for health and drug benefits during the follow-up period differed by patient, annualization as well as techniques of survival analysis (i.e., examination of data according to time observed without any specific threshold) were employed to estimate the above-described measures.

Data Source

Data were obtained from the proprietary database, which is comprised of fully adjudicated medical and pharmaceutical claims for nearly 27 million unique patients from 43 health plans across the United States. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats) as well as both community pharmacy and mail-order prescription records; available data on prescription records include the National Drug Code (NDC) as well as days supplied and quantity dispensed (for a subgroup of datasets). Both paid and charge amounts are available for all services rendered as well as dates of service for all claims. Additional data elements include demographic variables (age, gender, geographic region), plan type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

Records in the database are representative of the national managed care population on a variety of demographic measures, including geographic region, age, gender, and plan type. The data are also longitudinal, with an average member enrollment time of 2 years. Only health plans submitting data for all members are included in the database, ensuring complete data capture and unbiased samples. Data contributions are also subjected to a series of quality checks to ensure a standardized format and minimal error rates.

Measures

Measures of interest in these analyses included the incidence of all relapses as well as utilization and costs of MS-related medications and health care services during the period of follow-up. MS relapses are typically defined using one of several disability or symptom scales. Analyses of claims data are limited, however, to measures that would be associated with care-seeking behavior. An operational definition of relapses was therefore employed and was defined on the basis of either (a) an inpatient claim (hospitalization) with a listed principal diagnosis of MS or (b) a claim for an outpatient visit with a listed diagnosis of MS in combination with a pharmacy or medical claim (within 7 days after the visit) for one of the following: intravenous methylprednisolone or corticotrophin or oral methylprednisolone, prednisone, prednisolone, or dexamethasone. If multiple claims were present within a 30-day window, this was treated as a single relapse event; the first available service date within such a grouping was deemed to be the relapse date.

Medications of interest included immunomodulatory therapy (i.e., 1A [NDC code 59627-0001-03, “J” code 1825], 1B [50419-0521-03, 50419-0521-15, J1830], and GA [00088-1150-03, Q2010]), as well as prescription medications indicated for control of MS symptoms and side effects of immunomodulatory therapy (e.g., antispasmodics, anticholinergics, corticosteroids).

Health care services included selected laboratory tests for monitoring of immunomodulatory therapy (i.e., complete blood counts [CPT code 85031, 85022-85025], platelet counts [85007, 85027, 85585, 85590, 85595], and liver function tests [80076, 82040, 82247, 82248, 84075, 84155, 84460, 84450]), outpatient services (i.e., emergency room, physician office, home health, imaging [i.e., MRI], and other hospital outpatient visits), and hospitalizations for MS. Inpatient and outpatient services were deemed to be MS-related based on a relevant listed diagnosis (principal or secondary); lab tests were included regardless of diagnosis. Costs of all relevant medications and services were assessed. A health plan perspective was adopted in these analyses; cost estimates were therefore based on the amount paid (less patient copayments and deductibles) for relevant claims.

Analyses

Primary analyses were conducted on an intent-to-treat basis; all patients with an MS diagnosis and receipt of immunomodula-
therapy were therefore included in these analyses. Additional analyses focused attention on important subgroups, including patients newly starting immunomodulatory therapy as well as those remaining on only a single immunomodulatory medication (i.e., exclusive of switch or add-on therapy). New starts were determined based on the absence of any pharmacy claims for immunomodulatory therapy during a 9-month “pretreatment” period (i.e., prior to the first claim for the medication of interest).

Patients in the 3 treatment groups were first compared with respect to a variety of demographic and clinical characteristics, including age, gender, duration of follow-up, number of relapses and total costs during the pretreatment period (new starts only), type of health plan (e.g., PPO, HMO, fee-for-service), physician specialty, and geographic region.

Estimated propensity scores for use of immunomodulatory therapy also were calculated as a measure of patient severity of illness and disease progression. These scores represent a given patient’s probability, or “propensity,” of receiving a given treatment option and are calculated by summing coefficient values for a list of potential confounding variables. Use of these scores confers the advantage of having a single estimate available to adjust for confounding (i.e., effects on the findings of interest other than treatment effect) in any multivariate analysis, and have been widely used in clinical and economic research examining causal effects and in comparisons of nonrandomized groups.28,29 In this case, the outcome of interest was the probability of use of any of the 3 immunomodulatory medications of interest. Covariates (i.e., potentially confounding variables) were introduced to the model using stepwise logistic regression techniques; those achieving significance at a level of \( P < .10 \) were retained. In the final model, age, geographic region, a flag for the presence of at least one relapse during the pretreatment and follow-up periods, physi-
Clinical and Economic Impact of Glatiramer Acetate Versus Beta Interferon Therapy Among Patients With Multiple Sclerosis in a Managed Care Population

<table>
<thead>
<tr>
<th>Measure</th>
<th>Glatiramer Acetate (n=1,674)</th>
<th>Interferon Beta-1a (n=5,031)</th>
<th>Interferon Beta-1b (n=1,752)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence (rate/1,000 person-years)</td>
<td>291.2</td>
<td>314.4</td>
<td>241.1</td>
<td></td>
</tr>
<tr>
<td>Time to first relapse, days (mean, SD)</td>
<td>193.7 (160.1)</td>
<td>189.9 (163.1)</td>
<td>187.8 (157.1)</td>
<td></td>
</tr>
<tr>
<td>Risk of relapse at one year (relative to glatiramer acetate)*</td>
<td>–</td>
<td></td>
<td></td>
<td>1.147</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.512</td>
</tr>
</tbody>
</table>

*Hazard rates were calculated using Cox proportional hazards models, controlling for propensity scores and duration of follow-up.

Results

Patient Characteristics

Demographic and clinical characteristics of the study sample are presented in Table 1. A total of 8,457 patients were selected for inclusion in these analyses (n=1,674, 5,031, and 1,752 for GA, 1A, and 1B, respectively). The mean age for the sample was 42 years; approximately 75% were female. Both age and gender differed significantly (P<.001) by treatment group. The mean duration of follow-up (approximately 520 days or 17.3 months for the overall sample) also differed significantly (P<.001) by group and was substantially lower among patients receiving GA versus those receiving the other drugs; this phenomenon is likely due to GA’s later introduction to the MS marketplace. As a result, unadjusted information on relapse, utilization, and costs is presented on an annualized basis.

Mean propensity scores for use of immunomodulatory therapy were highest for GA patients (0.2631 versus 0.2575 and 0.2431 for 1A and 1B, respectively). Significant (P<.001) differences also were noted for plan type, physician specialty, and geographic region. Patients receiving GA were more likely to be members of more managed plans (e.g., HMO, PPO), while those receiving 1A and 1B were somewhat more likely to be in less managed environments (e.g., indemnity, POS). Nearly two thirds of patients receiving immunomodulatory therapy were managed by a neurologist.

Among patients receiving GA, there were no switches to or polytherapy with either of the beta interferons. However, a total of 498 (9.9%) and 96 (5.5%) 1A and 1B patients, respectively, switched or added therapy during follow-up. The majority of these therapy changes involved GA (i.e., either as switch or add-on therapy).

Of all identified patients receiving immunomodulatory therapy, a total of 3,161 (37.4%) were identified as new starts (i.e., based on a 9-month pretreatment period with no use of such medication). Among these patients, the mean (±SD) number of relapses during pretreatment did not significantly differ by treatment group (0.22 ±0.64) for GA versus 0.30 ±0.88 and 0.30 ±0.82 for 1A and 1B, respectively; P=.064). Mean costs during this period were significantly different, however, and were lowest for GA ($13,018 versus $14,853 and $16,697 for 1A and 1B, respectively; P=.003).
Relapse Rates

Information on relapse rates is presented in Table 2. The cumulative incidence of all relapses during follow-up was 291.2, 314.4, and 241.1 per 1,000 person-years for GA, 1A, and 1B respectively. Time to first relapse was somewhat longer among patients receiving GA (193.7 [±160.1] days versus 189.9 [±163.1] and 187.8 [±157.1] for 1A and 1B, respectively); correspondingly, the adjusted one-year risk of relapse was significantly (P<.005) higher for the beta interferons relative to GA (HR = 1.147 and 1.512 for 1A and 1B, respectively).

MS-related Resource Utilization

Utilization of MS-related medications and health care services is presented in Table 3. Other than study therapy, most other medications were used infrequently. The most commonly used medications were antidepressants (mean number of prescriptions per year: 2.5 to 2.7), skeletal muscle relaxants (1.6 to 1.9), and adrenals and combinations (1.3 to 1.7). Surprisingly, while periodic laboratory monitoring is recommended for the beta interferons but not for GA, the use of selected tests was infrequent among all groups and did not materially differ between
them. Utilization of other services also is presented in Table 3. Use of physician office and other hospital outpatient services was highest among 1A patients, while use of inpatient services (i.e., for treatment of relapse and other MS-related services) was slightly higher among GA patients.

**MS-related Costs**

Annualized costs of medications and health care services are presented in Table 4. Mean (±SD) costs of all MS-related medications were lowest for GA ($7,256 ±$5,727), followed by 1A ($7,992 ±$6,219) and 1B ($8,083 ±$6,260); these differences were statistically significant (*P* <.001). GA’s lower costs relative to the beta interferons were manifested almost entirely in lower acquisition costs for study therapy. Costs of outpatient services were similar for GA and 1A and slightly lower for 1B. Costs for inpatient care were lowest for 1A relative to the other 3 groups; neither outpatient nor inpatient costs differed statistically. Total costs of care averaged $9,522 (±$9,706), $9,957 (±$9,083), and $10,185 (±$9,526) for GA, 1A, and 1B, respectively (*P* =.004), which again primarily reflects differences in immunomodulatory drug costs. Findings persisted in multivariate analyses of cost; differences were mitigated somewhat between GA and 1A, while differences between GA and 1B were more marked ($10,879, $10,968, and $11,619 for GA, 1A, and 1B, respectively).

**Additional Analyses**

Among patients newly starting immunomodulatory therapy, the incidence of all relapses during follow-up was 17% to 22% higher with the beta interferons relative to GA (data not shown); while the one-year risk of relapse did not differ between 1A and GA, the risk among 1B patients was nearly double that of GA (HR=1.856, *P* =.020). Findings were similar among patients who did not switch or add on therapy (HR=1.389 for 1B relative to GA, *P* =.029).

Not surprisingly, in the cohort of patients newly starting immunomodulatory therapy, utilization of health care services was somewhat lower than for the entire cohort, particularly with respect to inpatient care; utilization of MS-related medications was similar, however (data not shown). On an annualized basis, total costs for GA patients remained lower than for 1A and 1B patients ($9,646 ±$10,209) versus $9,979 ±$10,815 and $10,553 ±$12,140, respectively); on an adjusted basis, costs for GA and 1A were similar ($11,310 and $11,192, respectively), and reduced relative to 1B ($12,347).

**Discussion**

To examine the impact of use of GA therapy on relapse rates as well as MS-related resource utilization and costs relative to that among patients receiving beta interferon 1A or 1B, we undertook a retrospective analysis of medical and pharmacy claims data among a cohort of MS patients receiving these medications. Data on the incidence of relapses was examined for these patients, as was information on the utilization and costs of MS-related medications, outpatient services, and inpatient care.

The results of this study indicate that use of GA therapy in patients with MS results in a lower rate of relapse relative to those receiving either beta interferon therapies. In addition, therapy with GA appeared to be more “durable” than that of the beta interferons—patients receiving the former did not switch or add on immunomodulatory therapy, while nearly 10% of those receiving beta interferon therapy did experience a therapy change. Finally, total costs of MS-related care were reduced by $400 to $700 among GA patients relative to the beta interferons; findings persisted in multivariate analyses controlling for age, sex, and propensity scores for immunomodulatory therapy.

A number of previous studies have evaluated the cost-effectiveness of immunomodulatory therapy in multiple sclerosis. Without exception, all of the existing studies have compared the costs and effects of beta interferon or GA therapy to those among patients receiving symptomatic relief only. To the best of our knowledge, this is the first such study to com-

---

**TABLE 4 Costs of MS-related Medications and Health Care Services by Treatment Group**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Glatiramer Acetate (n=1,674)</th>
<th>Interferon Beta-1a (n=5,031)</th>
<th>Interferon Beta-1b (n=1,752)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study therapy</td>
<td>$6,740 ($3,301)</td>
<td>$7,547 ($3,856)</td>
<td>$7,648 ($3,968)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other MS-related medications</td>
<td>$516 ($420)</td>
<td>$445 ($365)</td>
<td>$435 ($292)</td>
<td>.764</td>
</tr>
<tr>
<td>TOTAL medications</td>
<td>$7,256 ($5,727)</td>
<td>$7,992 ($6,219)</td>
<td>$8,083 ($6,260)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>$1,291 ($2,998)</td>
<td>$1,202 ($3,171)</td>
<td>$1,083 ($2,603)</td>
<td>.459</td>
</tr>
<tr>
<td>Inpatient care</td>
<td>$975 ($5,575)</td>
<td>$763 ($4,029)</td>
<td>$1,019 ($4,992)</td>
<td>.168</td>
</tr>
<tr>
<td>TOTAL MS-related costs</td>
<td>$9,522 ($9,706)</td>
<td>$9,957 ($9,083)</td>
<td>$10,185 ($9,526)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Note: All cost measures are annualized.
pare clinical and economic effects among these medications specifically. Most economic studies that have been performed to date have concluded that use of immunomodulatory therapy results in a substantial increase in costs and only modest clinical effects. These findings are at odds with current clinical opinion, however, which suggests that immunomodulatory agents should receive widespread use among patients with MS and should be used early in the course of the disease.39

Limitations

We note some limitations of our analysis. First, our comparison was limited to patients receiving immunomodulatory therapy, as noted above. In reality, many MS patients are still treated with only medications for the symptoms; in fact, nearly 75% of the patients with MS diagnoses in our database did not receive immunomodulatory medications. Examination of the economic and clinical impact of immunomodulatory medications as a group in an MS population requires comparison to a comparable population that did not receive these medications. Such an analysis is likely to be problematic in a retrospective database, however, as patients not receiving immunomodulatory therapy are historically likely to be at an earlier stage of disease progression and therefore less severely ill.

In addition, as with all quasi-experimental research based on retrospective data, we cannot rule out the possibility that our findings may have been influenced by differences in disease severity, duration of illness, and rate of disease progression between the 3 treatment groups that were the focus of our analysis. While it is true that these important factors are not detectable in any detailed way in claims data, the use of a propensity score in this circumstance does provide a method to control for differences in patient, physician, or health plan characteristics between patient groups. Indeed, our findings were nearly identical among the subgroup of patients newly starting immunomodulatory therapy (who would be expected to be more comparable in terms of disease progression and/or severity) as well as those remaining on a single agent during follow-up. Perhaps most importantly, the direction of these findings was unchanged in multivariate analyses controlling for propensity for immunomodulatory therapy and other covariates that were detectable in this particular data source.

In addition, our measure of relapse was limited to utilization proxies only; this definition was likely insensitive or conservative since overall annualized relapse rates (0.24 to 0.31 per patient) are lower than those reported in clinical studies.41-36 However, this effect was equally distributed across treatment groups and therefore likely affects only the magnitude (and not the direction) of our findings. While GA appeared to confer therapeutic benefit with regard to relapse as measured in our study, it should be noted that differences in risk and time to event were moderate (albeit statistically significant); perceptions as to the clinical significance of these differences will vary.

Finally, we could not measure the impact of these medica-

DISCLOSURES

Funding for this research was provided by Teva Neuroscience, Inc., U.S., a subsidiary of Teva Pharmaceutical Industries, Ltd., manufacturer of glatiramer acetate. Author Merri Kay Oleen-Burkey is employed by Teva Neuroscience, Inc. Authors Daniel A. Olendrow and Evgenia Jilinskaia are employed by PharMetrics, Inc., a health care data and research company that has consulting contracts with Teva Neuroscience. Funding was obtained by Olendrow. Ollendorf served as principal author of the study. Study concept and design and drafting of the manuscript were contributed primarily by Ollendorf and Oleen-Burkey. Critical revision of the manuscript was the work of Jilinskaia. Administrative, technical, and/or material support was provided by PharMetrics.

REFERENCES


Clinical and Economic Impact of Glatiramer Acetate Versus Beta Interferon Therapy Among Patients With Multiple Sclerosis in a Managed Care Population