Therapeutic Interferon Interchange in Relapsing Multiple Sclerosis Lowers Health Care and Pharmacy Expenditures with Comparable Safety

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ABSTRACT

Introduction: For patients with a less-active (fewer relapses or complete recovery from relapses, less radiologic burden of disease, or no or limited disease-related disability) relapsing form of multiple sclerosis (MS), interferon (IFN) beta-1b subcutaneous is similar in efficacy to IFN beta-1a intramuscular and subcutaneous. The purpose of this study was to assess the impact of patient interchange from an IFN beta-1a to IFN beta-1b.

Methods: This was a retrospective, pre-post study of adult patients with relapsing MS who underwent interchange from an IFN beta-1a to IFN beta-1b between April 15, 2014, and April 30, 2015. Health care financial and utilization outcomes between the 6 months before and after interchange were compared, and safety outcomes after interchange were assessed.

Results: A total of 36 primarily white, middle-age, and female patients underwent interchange. Monthly total health care and pharmacy expenditures decreased by approximately 40% and 44%, respectively, from pre-to-post interchange ($p < 0.001$). Health care utilization was unchanged ($p < 0.05$). Seven (43.8%) patients underwent interchange back to IFN beta-1a intramuscular. No patients underwent interchange back to IFN beta-1a subcutaneous. The most common adverse effect reported after interchange was injection-site reaction.

Conclusion: Health care expenditures decreased and adverse effects were limited among patients with MS who underwent an interchange from an IFN beta-1a to IFN beta-1b. These findings suggest that a therapeutic interchange between IFNs for patients with less-active MS disease is well tolerated. Further research is needed to determine the impact of such an interchange on disease progression.

INTRODUCTION

Multiple sclerosis (MS) is a disease of the central nervous system and is characterized by demyelination and neurodegeneration of the brain, spinal cord, or optic nerves.[1] MS has been categorized into 4 types: Relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing.[1] Medications are approved only to treat relapsing forms of the disease with the exception of ocrelizumab, which was approved in 2017 for primary-progressive MS.[2]

There are currently 14 US Food and Drug Administration-approved disease-modifying therapies available.[3] The first medications approved for the treatment of MS were self-injectables including interferon (IFN) beta-1a and IFN beta-1b and glatiramer acetate. Despite approvals of other medications during the last 10 years, use of self-injectable medications continues in treatment for relapsing MS, particularly for patients with less-active disease (fewer relapses, complete recovery from relapses, less radiologic burden of disease, no or limited disease-related disability, etc). Self-injectables remain the mainstay of MS treatment because the long-standing history of their use provides a wealth of information related to their safety and efficacy.[4,5]

IFN beta-1a is available as a once weekly intramuscular (IM) injection (IFN beta-1a IM) and a thrice-weekly subcutaneous (SC) injection (IFN beta-1a SC).[6,7] IFN beta-1b is available as an every-other-day SC injection (IFN beta-1b SC) under the brands Betaseron (Bayer Healthcare Pharmaceuticals Inc, Whippany, NJ) and Extavia (Novartis, East Hanover, NJ).[8,9] For the treatment of relapsing forms of MS, the choice of injectable medication typically is made on the basis of mode, frequency of administration, safety, and tolerability. Choice often is driven by patient preference because these medications have similar efficacy as demonstrated in both randomized and nonrandomized head-to-head trials.[10-15] Results of 2 IFN head-to-head trials, INCOMIN and EVIDENCE, demonstrated better efficacy with IFN beta-1b SC and IFN beta-1a SC, respectively, over IFN beta-1a IM.[14-15] However, because of substantial limitations in study designs and inconsistent findings vs phase 3 trial findings, results of these studies do not support the use of one IFN over another solely based on efficacy.[16]

Despite MS prevalence and the number of approved disease-modifying therapies, updated national treatment guidelines are lacking.[17] Neurology health care practitioners at Kaiser Permanente (KP) Colorado (KPCO) created an evidence-based consensus and treatment algorithm to improve the care of KPCO members with MS. The algorithm takes a risk-stratified approach to tailor patient therapy on the basis of clinical parameters and identifies preferred disease-modifying therapy based on KP-specific prices obtained through

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contracting. Patients with low-risk prognostic features (eg, lower frequency/number of relapses, no/low level of disability, fewer than 2 spinal cord lesions, fewer than 2 gadolinium-enhancing lesions, absence of severe motor/cerebellar/brainstem involvement) are risk stratified into the less-active relapsing MS category.[4-5] For these patients, IFN beta-1b SC (Extavia; Novartis, East Hanover, NJ) is the preferred formulary self-injectable medication based on similarities in efficacy to IFN beta-1a IM, IFN beta-1a SC, and glatiramer acetate.[10-15,18-24]

Canadian MS Working Group recommendations state a lateral interchange between IFNs and glatiramer acetate may be necessary in situations involving poor tolerability but also for nonclinical reasons such as change in insurance coverage.[5] However, little real-world evidence exists on the effects of interchange between IFN beta-1a IM/SC and IFN beta-1b SC for nonclinical purposes. This study's objective was to determine the clinical, economic, and safety ramifications of patient interchange in the setting of relapsing forms of MS from an IFN beta-1a product to IFN beta-1b SC.

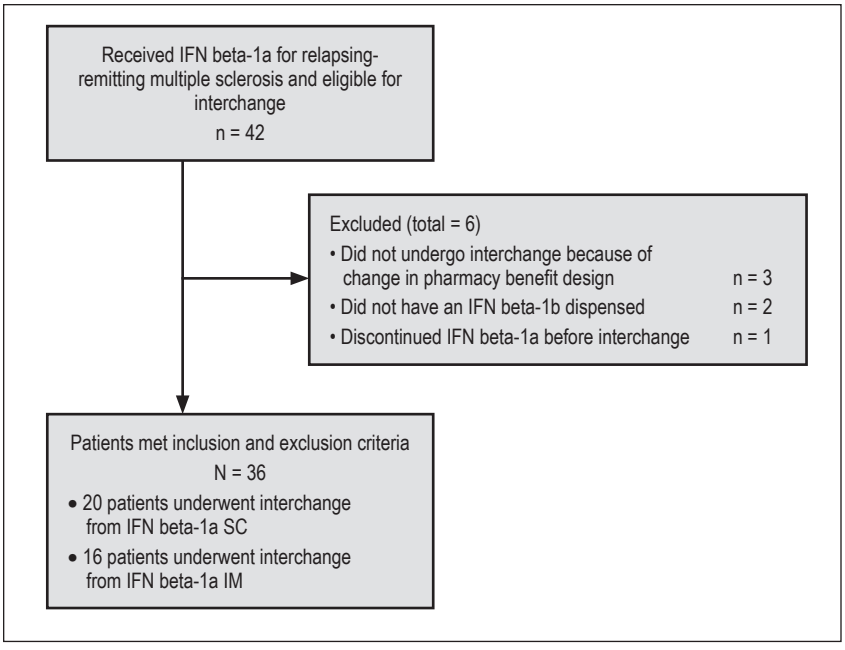

Figure 1. Patient dispositions.
IFN = interferon; IM = intramuscular; SC = subcutaneous.

METHODS

Study Design and Setting

This was a retrospective, pre-post, 1-sample study conducted at KPCO, an integrated health care delivery system that provides care for more than 660,000 members in Colorado. At the time of the study, 2 of the 30 KPCO medical offices had a neurology specialty clinic. The clinics employed 13 neurologists, 5 registered nurses, and 2 dedicated clinical pharmacy specialists (CPS). Patients with MS who were prescribed an IFN beta-1a were contacted and underwent interchange to IFN beta-1b SC with approval from their prescribing neurologist between April 15, 2014, and April 30, 2015. This study was conducted retrospectively after the intervention was performed. Patients were followed for 6 months after interchange.

KPCO's electronic medical record provides e-prescribing capabilities and captures coded and free-text information. KPCO also has extensive administrative databases that contain medical, pharmacy, laboratory, Emergency Department (ED), hospitalization, membership, and death information obtained internally from within the health system and from other contracted and affiliated facilities. KPCO owns and operates pharmacies at which its members can purchase subsidized prescription medications as well. Information on such purchases is captured in the KPCO administrative pharmacy database. KPCO also maintains a decision-support system (Value Tracker, Kaiser Permanente, Oakland, CA) that gathers and compiles health care expenditures for KPCO members using both claims and internal service utilization algorithms. All aspects of this study were reviewed and approved by the KPCO institutional review board.

Study Population

Patients with relapsing MS were included if they underwent an interchange from an injectable IFN beta-1a to IFN beta-1b SC between April 15, 2014, and April 30, 2015, were a KPCO Denver/Boulder commercial Health Plan member, had received an IFN beta-1a for 6 months before interchange, and were age 18 years or older. Patients were excluded if they did not have 6 months of KPCO membership before the interchange. Criteria for interchange included no previous IFN failure and no high-risk features for early progression (Sidebar: Criteria for Interchange from Interferon beta-1a Intramuscular Injection to Interferon beta-1b Subcutaneous Injection).

Intervention

The KPCO Neurology Department developed a protocol with which patients

Criteria for Interchange from Interferon beta-1a Intramuscular (IM) Injection to Interferon beta-1b Subcutaneous (SC) Injection

- Medication prescribed by Kaiser Permanente Colorado neurologist
- Patient with relapsing form of multiple sclerosis
- No contraindication, serious precaution, or past intolerance to IFN beta-1b SC
- Not prescribed IFN beta-1a IM to assist with adherence issues
- Has not failed interferon therapy by disease progression
- Does not have high-risk features for early progression to secondary-progressive multiple sclerosis or high-risk features while on a disease modifying therapy

could undergo interchange from either IFN beta-1a IM or IFN beta-1a SC (index IFN) to IFN beta-1b SC as both a quality and cost-savings initiative. All patients who were receiving an IFN beta-1a injectable were identified, and an extensive chart review was conducted by a CPS to determine if interchange to IFN beta-1b SC was appropriate. Each interchange-eligible patient's neurologist was contacted for interchange approval before patient outreach. Upon neurologist approval, each patient was contacted by a CPS who provided education regarding the interchange. Patients could opt to remain on their index IFN for an increased copayment/co-insurance amount. Patients completed their existing IFN beta-1a prescription and initiated IFN beta-1b SC when their next IFN prescription was dispensed. Laboratory monitoring was not part of this interchange but was performed on the basis of routine Neurology Department protocols for monitoring of IFN medications.

Study Outcomes

The primary outcome was a 6-month preinterchange-to-postinterchange comparison of patients' monthly total health care expenditures in 2014 dollars from the perspective of KPCO. Six months of follow-up was chosen as the interval with which to focus outcomes on medication tolerability and impact on health care expenditures after interchange. Total health care expenditures were chosen because all aspects of care would be captured (eg, pharmacy dispensings, laboratory measures, imaging services, medical services) and would indicate the totality of use within the health care system. Secondary outcomes included 6-month pre-post comparisons of pharmacy expenditures, health care utilization, and IFN adherence. Tertiary outcomes included descriptions of rates of safety parameters including adverse drug reactions, therapy escalation, and interchange to other MS therapies during the 6-month postperiod. Flulike symptoms and injection-site reactions were observed during 2 periods of time (0-3 months and 4-6 months) because these adverse reactions have the potential to improve over time.[8] Tertiary outcomes were reviewed only during the postperiod because patients had to have stable MS disease before interchange as determined through a clinical review performed by a CPS and a neurologist that included an assessment of MRI findings, relapse history, symptom stability, etc. Patients who underwent interchange back to their index IFN were assessed for safety parameters during the time they were receiving either IFN during the postinterchange period.

Table 1. Patient characteristics

Characteristic	Value (N = 36)
Age, years, mean (SD)	51.2 (8.4)
Women, n (%)	30 (83.3)
Years since MS diagnosis, mean (SD)	13.9 (8.4)
Race, n (%)	
White	33 (91.6)
African American	1 (2.7)
Unknown/unreported	2 (5.6)
IFN beta-1a type, n (%)	
IFN beta-1a IM	16 (44.4)
IFN beta-1a SC	20 (55.6)

IFN = interferon; IM = intramuscular; MS = multiple sclerosis; SC = subcutaneous; SD = standard deviation.

Data Collection

Data were collected from the KPCO administrative database and manual electronic medical record review queries. Information on patient date of birth, sex, KPCO membership and benefit design, race, and medical office and ED visits was collected electronically. Information on MS diagnosis and adverse drug reactions was collected through a manual review of the electronic medical record. Health care and pharmacy expenditures were collected from Value Tracker. Information on medication dispensing was collected from the electronic pharmacy database.

Data Analysis

In 2014 dollars, the mean annual total health care expenditure per patient with MS who received either IFN beta-1a IM or IFN beta-1a SC was $34,224 (± $51,336).[25] After interchange, a 33% reduction in 6-month total health care expenditures was estimated. With 80% power; an alpha of 0.05; and a 1-sample, 2-sided equality design, the study would need at least 17 patients to detect the hypothesized reductions in 6-month total health care expenditures.

Patient age was determined as of the interchange date. IFN adherence was calculated as the percentage of days covered for any injectable IFN. Patient characteristics, risk factors, and outcomes were reported as means, medians, and standard deviations for interval level and percentages for nominal- and ordinal-level data. Expenditures were log-transformed before analysis to account for any data skewness. Outcomes were compared between time periods with McNemar's tests of association for nominal data and 1-sample *t*-tests for interval-level data.

RESULTS

Thirty-six patients met criteria and were evaluated (Figure 1). Participants primarily were white, middle-age, female, and at approximately 14 years since MS diagnosis at the time of interchange (Table 1). Mean monthly total health care ($3682 pre vs $2211 post) and pharmacy ($3334 pre vs $1869 post) expenditures decreased significantly between the pre- and postinterchange periods ($p < 0.001$) (Table 2). Although the mean monthly counts of ambulatory (0.4 pre vs 0.5 post) and MS-related ambulatory visits (0.1 pre vs 0.2 post) and percentage of patients

Table 2. Economic and clinical outcomes according to pre- and postinterchange period

Outcome	Preinterchange	Postinterchange	p value
Monthly total health care expenditures,[a] mean, $US (SD)	$3682 ($851)	$2211 ($1301)	< 0.001
Mean monthly pharmacy expenditures,[a] $US (SD)	$3334 ($771)	$1869 ($1061)	< 0.001
Monthly ambulatory visit count, mean (SD)	0.4 (0.4)	0.5 (0.6)	0.270
Monthly MS-related ambulatory visit count, mean (SD)	0.1 (0.1)	0.2 (0.2)	0.098
At least one ED visit, n (%)	0 (0)	2 (5.6)	0.564
At least one MS-related ED visit, n (%)	0 (0)	1 (2.6)	0.758
Percentage of days covered for any IFN, mean (SD)	88.7 (17.8)	92 (15.1)	0.126

[a] From the perspective of Kaiser Permanente Colorado.
ED = Emergency Department; IFN = interferon; MS = multiple sclerosis; SD = standard deviation.

with at least one ED (0.0% pre vs 5.6% post) and MS-related ED (0% pre vs 2.6% post) visit numerically increased, these numbers did not reach statistical significance (all $p < 0.05$). Although not statistically significant, a trend toward improved mean IFN percentage of days covered was observed between the pre- (88.7%) and postinterchange (92%) ($p = 0.126$). Patients who underwent interchange back to their index IFN experienced a similar mean percentage of days covered between pre- (91.7%) and postinterchange (100%) ($p = 0.217$) as patients who did not undergo an interchange back (88.1% pre vs 90% post, $p = 0.352$).

The most common adverse effect reported was injection-site reaction for both index IFNs (Table 3). Leukopenia was observed in 1 patient whose index IFN was IFN beta-1a SC; however, leukopenia was present before interchange and did not necessitate a change in therapy postinterchange. No other laboratory abnormalities were identified.

By the end of the 6-month postinterchange period, 7 of 16 (43.8%) patients underwent interchange back to IFN beta-1a IM (Table 3). The most common reason for interchange back to IFN beta-1a IM was injection-site reaction, and interchange back occurred at approximately 2 months after interchange from their index IFN (Table 4). No interchanges to index IFN were observed in patients who initially underwent interchange from IFN beta-1a SC. No patients underwent interchange to another MS agent.

DISCUSSION

This pre-post evaluation of 36 patients with stable, relapsing MS who underwent an interchange from an IFN beta-1a product to IFN beta-1b SC revealed reduced health care expenditures without substantial medication-related adverse effects. Increasing health care expenditures are a marker of worsening health, whereas decreasing/equivalent health care expenditures are a marker of stable health. Our findings suggest that patients experienced disease stability after interchange from IFN beta-1a to IFN beta-1b SC even though they needed more weekly injections after undergoing interchange. These findings suggest that interchange to a preferred formulary agent can increase MS affordability. As total health care costs of MS treatment rise and medication costs comprise approximately 65% of total expenditures,[25] an evidence-based approach to the management of relapsing MS is essential. The American Academy of Neurology has recognized the need for data including head-to-head trials and cost-effectiveness analyses.[26]

Our findings are consistent with previous studies that described no significant differences in safety and efficacy between IFN beta-1a and IFN beta-1b. Randomized, double-blind, placebo-controlled trials have demonstrated similar reductions in both 2-year relapse rates and active lesions by IFN.[18-21] Head-to-head comparisons of self-injectable medications (eg, IFN beta 1-b and glatiramer acetate) identified no differences in MS relapse and lesion outcomes.[10-15]

The statistically significant 40% decrease in total health care expenditures suggests disease stability after interchange (ie, expenditures likely would have increased if disease burden intensified because patients would have used additional health care resources). The total decreases in expenditures occurred even though 7 patients underwent interchange back to their index IFN, specifically IFN beta-1a IM, which was a more expensive therapy than IFN beta-1b SC (likely because of our institution's favorable contract pricing for IFN beta-1b SC). On the basis of manual chart review, these reverse interchanges were attributable to injection-site reactions and flulike symptoms associated with IFN beta-1b SC. This finding

Table 3. Safety parameters during the 6 months after interchange to interferon beta-1b subcutaneous by index interferon agent

Parameter	Index IFN agent, no. (%)		Total incidence, no. (%) (N = 36)[a]
	Beta-1a intramuscular (n = 16)	Beta-1a subcutaneous (n = 20)	
Flulike symptoms at 0-3 months	2 (12.5)	1 (5)	3 (8.3)
Flulike symptoms at 4-6 months	0 (0)	0 (0)	0 (0)
Injection-site reactions at 0-3 months	8 (50)	6 (30)	14 (38.9)
Injection-site reactions at 4-6 months	0 (0)	5 (25)	5 (13.9)
Leukopenia	0 (0)	1 (5)	1/30 (2.8)
Thyroid abnormalities	0 (0)	0 (0)	0/17 (0)
Hepatic injury	0 (0)	0 (0)	0/29 (0)
Worsening depression	1 (6.3)	0 (0)	1 (2.8)
Interchanged to a highly active MS agent[b]	0 (0)	0 (0)	0 (0)
Underwent interchange back to index IFN agent	7 (43.8)	0 (0)	7 (19.4)
Underwent interchange to another MS agent[c]	0 (0)	0 (0)	0 (0)

[a] N = 36 unless otherwise indicated; laboratory monitoring results were not completed by all patients in the period 6 months after interchange.
[b] Natalizumab, fingolimod.
[c] Dimethyl fumarate, teriflunomide, glatiramer acetate.
IFN = interferon; MS = multiple sclerosis.

Table 4. Reasons and length of time to interchange back to index interferon agent[a]

Patient no.	Reason	Length of time (mo)
1	Fever and injection-site reaction	3
2	Injection-site reaction	3
3	Injection-site reaction	3
4	Injection-site reaction	2
5	Injection-site reaction	2
6	Injection-site reaction	1
7	Injection-site reaction	1

[a] All patients underwent interchange back to beta-1a intramuscular.

is consistent with previous studies that concluded IFN beta-1a IM is associated with fewer injection-site reactions than other subcutaneous self-injectables.[27-28] No patients underwent interchange back to IFN beta-1a SC from IFN beta-1b SC, which suggests that a thrice-weekly injection schedule is similarly tolerated as an every-other-day injection schedule. The trend toward improved IFN medication adherence suggests that the interchange was tolerated regardless of the potential for injection-site reactions. Although some patients experienced injection-site reactions (possibly because more weekly injections were required), this was an expected adverse effect of IFNs and was within the normal safety profile of these medications.[7-9]

Study limitations included a small sample size that likely was attributable to rigorous inclusion criteria for interchange participation. Even though the incidence of MS is estimated to be high in Colorado at 1 in 550 persons, it remains a relatively rare disease.[29] Despite our small sample size, we detected substantial decreases in monthly health care and pharmacy expenditures. We did not have laboratory values for all patients during follow-up. Patients may not have adhered to the schedule for repeat laboratory testing despite receiving notifications from the KPCO Neurology Department, and the Department's laboratory monitoring protocol only required annual thyroid monitoring. We could not assess disease progression because there was no standardized protocol regarding imaging frequency and no routine documentation of the Expanded Disability Status Scale or other patient-reported outcomes among prescribing neurologists. To overcome this deficiency, total health care expenditures were used as a surrogate marker of disease activity.

The EVIDENCE[14] and INCOMIN[15] studies compared low-dose IFN, IFN beta-1a IM, with a high-dose IFN, IFN beta-1a SC or IFN beta-1b SC, respectively. Although certain studies reveal fewer relapses for patients receiving a high-dose IFN, those studies had limitations including single blinding and clinical differences between groups at baseline.[14,15] No studies of interchange between IFN products in real-world practice have been identified; further research is needed to assess the impact of an IFN beta-1a-to-IFN beta-1b interchange on long-term disease progression.

The favorable contract KP established for IFN beta-1b SC over IFN beta-1a products through which IFN beta-1b SC became the preferred self-injectable option was a factor in reducing total health care expenditures after interchange. Because of insurance regulatory differences across KP Regions, not all Regions were able to place formulary restrictions (prior authorization) on IFN beta-1a products. Depending on a health system's treatment preferences and its ability to negotiate contract pricing, its preferred IFN product, and its ability to place formulary restrictions on medications, our results may or may not be applicable to health care systems beyond KPCO.

In light of this study's small sample size, we did not assess for safety parameters during baseline because we assumed that patients' conditions were stable on their MS injectable therapy. Consequently, this study did not evaluate changes in injectable safety profiles. The study population grew older during an almost-14-year disease duration; some patients may have been or were approaching the secondary progressive phase of MS even though they had a relapsing form of the disease at the time of interchange. With longer disease duration, these patients likely had a lower relapse rate, which made it difficult to detect changes in disease stability after interchange.[30] Finally, our 6-month follow-up may have been too brief to allow for clinically significant outcomes; medications can be evaluated for as long as 2 years to assess clinical outcomes.

CONCLUSION

After interchange from an IFN beta 1a to IFN beta-1b SC, patients with relapsing MS incurred lower total health care and pharmacy expenditures, did not use health care services more frequently, and experienced limited adverse drug reactions. These findings suggest that a therapeutic interchange between IFNs in patients with less-active MS disease was well tolerated. Further research is needed to confirm these findings in a larger sample size and evaluate the impact of such an interchange on long-term disease outcomes and patient preference. ❖

Disclosure Statement

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Take Account

The ways and means for putting medicine in order must take account of the conditions of life and work among the people whom it must serve.

— Walton H Hamilton, 1881-1958, American economist and law professor