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ORIGINAL RESEARCH

Assessment of malignancy risk in patients with multiple sclerosis treated with intramuscular interferon beta-1a: retrospective evaluation using a health insurance claims database and postmarketing surveillance data

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Background: Intramuscular interferon beta-1a (IFNβ-1a), a multiple sclerosis (MS) therapy that has been commercially available for over a decade, provides a unique opportunity to retrospectively assess postmarketing data for evidence of malignancy risk, compared with relatively limited data available for more recently approved therapies. Postmarketing and claims data were analyzed to determine the risk of malignancy in MS patients treated with intramuscular IFNβ-1a.

Materials and methods: The cumulative reporting rates of suspected adverse drug reactions coded to malignancy in the intramuscular IFNβ-1a global safety database were compared with malignancy incidence rates in the World Health Organization GLOBOCAN database. In addition, using data from a large US claims database, the cumulative prevalence of malignancy in MS patients treated with intramuscular IFNβ-1a was compared with non-MS population controls, MS patients without intramuscular IFNβ-1a use, and untreated MS patients. Mean follow-up was approximately 3 years for all groups, ie, 3.1 years for the intramuscular IFNβ-1a group (range 0.02–6.0 years), 2.6 years for non-MS population controls (range 0–6.0 years), 2.6 years for the intramuscular IFNβ-1a nonuse group (range 0.01–6.0 years), and 2.4 years for the untreated MS group (range 0.01–6.0 years).

Results: An estimated 402,250 patients received intramuscular IFNβ-1a during the postmarketing period. Cumulative reporting rates of malignancy in this population were consistent with GLOBOCAN incidence rates observed within the general population. The claims database included 12,894 MS patients who received intramuscular IFNβ-1a. No significant difference in malignancy prevalence was observed in intramuscular IFNβ-1a users compared with other groups.

Conclusion: Results from this evaluation provide no evidence of an increased risk of malignancy with intramuscular IFNβ-1a use.

Keywords: multiple sclerosis, malignancy, safety, intramuscular interferon beta-1a, postmarketing surveillance, claims

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. Although there is no cure for MS, treatment with disease-modifying therapies can improve the clinical course by reducing the frequency of relapses and, with some treatments, slow the accumulation of physical disability commonly associated with MS. Because patients are typically diagnosed between 20 and 40 years of age[1] and MS is a lifelong disease, MS patients may use immunomodulatory disease-modifying therapies

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for extended periods of time, which may affect some aspects of immunosurveillance.[2] Given that some malignancies could be affected by use of these immunomodulatory therapies, it is important to evaluate the effect of various disease-modifying therapies on malignancy risk beyond short-duration clinical trials.

The pathogenesis of MS is believed to involve an inappropriate immune response mediated by autoreactive lymphocytes within the central nervous system.[1] While the association between autoimmune disease and cancer is not fully understood, autoreactive T cells have been shown to influence both the prevention and the advancement of cancer.[3] The heightened immune system activity in MS may prevent the development of cancer, leading to a reduction in cancer risk in the MS population.[4] Any modification of the immune system, in particular one involving activation of T cells, therefore carries the potential of changing the occurrence of cancer. Lifestyle changes following a diagnosis of MS may also contribute to a lowered cancer risk.[5] Multiple studies have examined the relationship between MS and cancer risk,[5–12] and while a lower overall risk of developing cancer in patients with MS has been observed in some studies,[5,6,9,13] the majority of these analyses have concluded that there is no difference in the risk of developing malignancies between patients with MS and the general population.[7,8,10–12] In addition, a few studies have suggested an increased risk of developing site-specific cancers, such as breast cancer,[11] urinary cancer,[5] and brain cancer.[5]

Recent studies have also examined the risk of malignancy in MS patients who have been exposed to disease-modifying therapies.[4,14–16] The disease-modifying therapies evaluated in these studies (glatiramer acetate, interferon beta-1a [IFNβ-1a], and IFNβ-1b) have been commercially available for over 10 years. Results have suggested that there is no difference in risk for MS patients treated with disease-modifying therapies compared with the general population. However, a decreased risk of development of several types of cancer in patients treated with these therapies was observed in one study,[14] while another investigation found a nonsignificant trend of elevated risk of nonbreast cancers.[4]

Intramuscular IFNβ-1a (Avonex®; Biogen Idec, Weston, MA) is a first-line disease-modifying therapy administered weekly for treatment of relapsing forms of MS. Intramuscular IFNβ-1a was first approved for use in MS by the United States Food and Drug Administration in May 1996 and is currently approved for use in 89 countries. Safety information available from the pivotal clinical trials at the time of product approval did not suggest an increased risk of malignancy.[17,18]

A global safety database was utilized to capture all intramuscular IFNβ-1a safety data during the postmarketing period. Currently, 15 years of postapproval data are available to evaluate the risk of malignancy. Insurance claims data from health plans, which include information on patient demographics, diagnoses, medical procedures, laboratory testing, and pharmacy data, offer an additional opportunity to evaluate the risk of malignancy related to use of disease-modifying therapies.

In this evaluation, we aimed to assess the malignancy risk associated with intramuscular IFNβ-1a treatment in patients with MS using postmarketing surveillance data from a global product safety database along with data from a large US claims database. This paper provides postmarketing safety data for intramuscular IFNβ-1a-treated patients that have not previously been published.

Materials and methods

Descriptions of the two data sources and the corresponding analyses used in this evaluation are provided below.

Intramuscular IFNβ-1a global safety database

The intramuscular IFNβ-1a global safety database captures all suspected adverse drug reactions with intramuscular IFNβ-1a reported to Biogen Idec worldwide since product approval, including spontaneous reports, literature case reports, and serious suspected adverse drug reactions from the intramuscular IFNβ-1a clinical trials. Suspected adverse drug reactions are coded using Medical Dictionary for Regulatory Activities (MedDRA)[19] terminology. Any event confirmed by a health care provider is considered a suspected adverse drug reaction unless a causality assessment of "not related" is provided by the treating health care provider. In addition, a large number of potential adverse drug reactions are captured in the intramuscular IFNβ-1a global safety database during contact with patients through an intramuscular IFNβ-1a toll-free support phone line, a patient support service provided by Biogen Idec, and through other formal postmarketing initiatives, such as nurse training programs and home drug delivery.

A cumulative review was performed of all suspected adverse drug reactions coded to a malignancy using MedDRA coding from May 1996 through April 2011. Adverse drug reactions coded to the terms "cancer," "neoplasm," or "malignancy" were queried and evaluated. Benign neoplasms were removed from this analysis; only cases with terms coded to a malignancy were included. Person-years of exposure

were calculated based on monthly sales data from each country based on the assumption that 52 vials or syringes of intramuscular IFNβ-1a are equivalent to one person-year of exposure (ie, each vial or syringe is equivalent to a weekly dose of intramuscular IFNβ-1a).

The cumulative reporting rates of malignancies by primary site in the intramuscular IFNβ-1a global safety database were compared with the most recently reported age-standardized incidence rates for malignancies in the GLOBOCAN 2008 database.[20] GLOBOCAN, a project of the World Health Organization's International Agency for Research on Cancer, is a worldwide epidemiological cancer database that provides country-by-country estimates of the incidence of and mortality from major type of cancers within the general population.[20] Population-weighted averages of the national incidence rates (derived from population-based cancer registries) from the 2008 GLOBOCAN database for "more developed regions" (North America, Europe, Japan, Australia, and New Zealand) were used for comparison, because approximately 85% of the marketed product is distributed within these regions (Biogen Idec, data on file).

Insurance claims database

The second data source used in this evaluation was the i3 InVision™ Data Mart Multiplan (PharmaNet/i3, Princeton, New Jersey), a large US health insurance claims database covering approximately 77,000,000 lives from 48 plans across seven regions of the country. Claims data from July 2004 through June 2010 were analyzed, with diagnosis terms coded to International Classification of Disease (ICD-9) criteria. In order to minimize exposure misclassification, only subjects with pharmacy benefits were included in the analysis.

The objective of this analysis was to determine the cumulative prevalence of malignancy in MS patients using intramuscular IFNβ-1a and to make comparisons with non-MS population controls, intramuscular IFNβ-1a nonuse MS patients, and untreated MS patients. MS cases were limited to patients with at least two diagnosis codes for MS (ICD-9 340). Cases with at least one intramuscular IFNβ-1a prescription after the index MS diagnosis date (the date of the first diagnosis of MS in the database) were designated intramuscular IFNβ-1a use; those with an indicated MS treatment and/or immunosuppressive treatment but no intramuscular IFNβ-1a prescriptions at any time were designated intramuscular IFNβ-1a nonuse. Cases with no use of an indicated MS treatment and no immunosuppressive treatment were designated untreated MS. Immunosuppressive drugs included those that were most likely to be used by patients with MS (mitoxantrone, rituximab, cyclophosphamide, azathioprine, methotrexate, mycophenolate, and cladribine).

For each MS case, two population controls with no history of MS were selected from the database, matched on age, gender, and follow-up time. Each control was assigned the index date of the matched case for the purpose of longitudinal analyses. Follow-up time was calculated as the time in the database from the index MS diagnosis date for cases and their controls. Mean follow-up time was approximately 3 years for all groups.

The outcome was defined as more than one diagnosis code for malignancy in any position of the claim at least 30 days apart. More than one diagnosis code was required in order to increase the confidence that true malignancy cases were being captured. Table 1 provides the malignancy exclusion criteria applicable to each group.

To provide a measure of the magnitude of the differences, the prevalence odds ratio was calculated as the prevalence of malignancy in the intramuscular IFNβ-1a use group divided by the prevalence of malignancy in the comparison group. To indicate the strength of the association between prevalence estimates, 95% confidence intervals were calculated.

Table 1 Group definitions and malignancy exclusion criteria, i3 InVision Data Mart Multiplan analysis

Group name	Group definition	Malignancy exclusion criteria
IM IFNβ-1a use	Subjects with at least two ICD-9 codes for MS and at least one IM IFNβ-1a prescription after the index MS diagnosis date[a]	Subjects were not counted as a case of malignancy if there were at least two ICD-9 codes for the malignancy prior to the first IM IFNβ-1a prescription date
IM IFNβ-1a nonuse	Subjects with at least two ICD-9 codes for MS and no IM IFNβ-1a prescriptions at any time in the database	Subjects were not counted as a case of malignancy if there were at least two ICD-9 codes for the malignancy prior to the index MS diagnosis date[a]
Untreated MS	Subjects with at least two ICD-9 codes for MS who had no use of an indicated MS treatment and no immunosuppressive treatment at any time in the database	Subjects were not counted as a case of malignancy if there were at least two ICD-9 codes for the malignancy prior to the index MS diagnosis date[a]
Non-MS population control	Subjects with no history of MS anytime in the database	At least two ICD-9 codes for the malignancy prior to the index MS diagnosis date[a] of the matched case

Note: [a]Date of the first diagnosis of MS seen in the database.
Abbreviations: ICD-9, International Classification of Disease; IM IFNβ-1a, intramuscular interferon beta-1a; MS, multiple sclerosis.

All tests assumed a two-sided alternative hypothesis and a 0.05 significance level. A Bonferroni correction to adjust for multiple comparisons resulted in $\alpha < 0.002$. All analyses were conducted using SAS/STAT® software, version 9.2.

Non-MS population controls were already age-matched by definition; when a subset of the population was analyzed (case versus case), MS groups were frequency-matched based on age to ensure that age distributions between the MS case comparisons were similar. Malignancies were grouped based on the cancer site categories used in GLOBOCAN 2008.

Results

Intramuscular IFNβ-1a global safety database

From May 1996 to April 2011, it was estimated that approximately 402,250 patients received intramuscular IFNβ-1a treatment with the marketed product, including 261,000 patients from the US and 141,250 patients from other countries in which intramuscular IFNβ-1a is approved, corresponding to approximately 1,492,407 person-years of exposure. For calculating rates of breast, ovarian, cervical, vaginal, and uterine carcinomas, the estimated female exposure to intramuscular IFNβ-1a was 81% of 1,492,407 person-years (1,208,849 woman-years) (Biogen Idec, data on file). For calculating rates of prostate and testicular carcinomas, the estimated exposure was 283,558 man-years (Biogen Idec, data on file).

The cumulative reporting rates by type of malignancy for all suspected reactions within the intramuscular IFNβ-1a global safety database were consistent with the incidence rates for malignancies in the GLOBOCAN database (Table 2). Based on the case reports that included case detail, the histological type, stage, and course of malignancies did not appear unusual for the patients' age, gender, and known risk factors.

Table 2 Comparison of cumulative reporting rates for suspected reactions coded to malignancies by primary site in the intramuscular IFNβ-1a global safety database with GLOBOCAN 2008 incidence rates for more developed regions[a]

Primary site of malignancy	Cumulative reporting rate of suspected reactions (per 100,000 person-years), 95% CI	GLOBOCAN 2008 incidence rates (age-standardized) for malignancies in more developed regions[a] (per 100,000 person-years)	
		Female	Male
Bladder	0.74 (0.4–1.3)	3.6	16.3
Brain, nervous system	1.34 (0.8–2.0)	4.4	5.8
Colorectal	3.35 (2.5–4.4)	24.3	37.7
Esophageal	0.34 (0.1–0.7)	1.3	6.5
Hodgkin lymphoma	0.47 (0.2–0.9)	1.9	2.2
Kidney	1.14 (0.7–1.8)	5.9	11.9
Laryngeal	0.00	0.6	5.4
Leukemia	2.14 (1.5–3.0)	5.9	9.1
Liver	0.54 (0.3–1.0)	2.7	8.2
Lung	3.02 (2.2–4.0)	18.8	47.1
Melanoma of skin[b]	1.88 (1.3–2.7)	8.7	9.6
Multiple myeloma	0.20 (0.05–0.6)	2.2	3.3
Nasopharyngeal	0.07 (0.003–0.3)	0.2	0.6
Non-Hodgkin lymphoma	1.54 (1.0–2.3)	7.1	10.3
Other pharyngeal	0.40 (0.2–0.8)	0.8	4.5
Oral cavity	0.47 (0.2–0.9)	2.3	6.8
Pancreas	0.60 (0.3–1.1)	5.5	8.3
Stomach	0.20 (0.05–0.6)	7.3	16.7
Thyroid	1.74 (1.2–2.5)	9.2	2.9
Breast (females)[b]	13.9 (11.9–16.1)	66.4	n/a
Cervix (females)[b]	0.83 (0.4–1.5)	9.1	n/a
Ovary (females)	0.91 (0.5–1.6)	9.3	n/a
Uterine (females)	1.08 (0.6–1.8)	13.0	n/a
Prostate (males)	4.58 (2.5–7.6)	n/a	61.7
Testicular (males)	0.35 (0.02–1.7)	n/a	4.6
All sites but nonmelanoma skin[c]	37.05 (34.1–40.2)	226.3	299.2

Notes: [a]More developed regions defined as North America, Europe, Japan, Australia, and New Zealand; [b]does not include noninvasive cancers (breast cancer in situ, cervical cancer stage 0, and melanoma stage 0), which did not fall into a GLOBOCAN category; [c]does not include basal cell cancer (17), squamous cell cancer (10), skin cancer (1), and skin cancer metastatic (1), which did not fall into a GLOBOCAN category.

Abbreviations: CI, confidence interval; IM IFNβ-1a, intramuscular interferon beta-1a; n/a, not applicable.

Insurance claims database

From July 2004 through June 2010, a total of 95,420 MS cases were identified in the claims database. Of these, 12,894 were classified as intramuscular IFNβ-1a users. The average age of subjects in this analysis was 46 years for all groups: 44.5 years for the intramuscular IFNβ-1a group (range 5.0–80.0 years), 44.5 years for non-MS population controls (range 5.0–80.0 years), 44.9 years for the intramuscular IFNβ-1a nonuse group (range 1.0–82.0 years), and 45.4 years for the untreated MS group (range 1.0–82.0 years). Seventy-seven percent of subjects were female. Mean follow-up time in the database was approximately 3 years for all groups: 3.1 years for the intramuscular IFNβ-1a group (range 0.02–6.0 years), 2.6 years for non-MS population controls (range 0–6.0 years), 2.6 years for the intramuscular IFNβ-1a nonuse group (range 0.01–6.0 years), and 2.4 years for the untreated MS group (range 0.01–6.0 years). The mean duration of treatment for the intramuscular IFNβ-1a group was 3.0 years (range 0.0–6.0 years).

When malignancy prevalence in the intramuscular IFNβ-1a use group was compared with that in non-MS population controls, no significant increase in the prevalence of malignancy in the intramuscular IFNβ-1a use group was observed (Table 3). Similarly, when the malignancy prevalence in the intramuscular IFNβ-1a use group was compared with the prevalence in MS patients with no use of intramuscular IFNβ-1a and in untreated MS patients, no significant increase was observed (Tables 4 and 5, respectively).

Discussion

Results from the evaluation of two data sources are consistent and provide no evidence of an increased risk of malignancy associated with intramuscular IFNβ-1a use. The reported rates of malignancies within the intramuscular IFNβ-1a global safety database were similar to the reported incidence rates in GLOBOCAN for the general population. The frequency and types of malignancies reported were similar to those observed within the general population. Cases were also reviewed to evaluate malignancies commonly associated with immunosuppression, such as high-grade lymphoid malignancies, Kaposi sarcoma, multiple nonmelanoma skin

Table 3 Malignancy in MS patients after IM IFNβ-1a use (n = 12,894) compared with non-MS population controls (n = 25,786), i3 InVision Data Mart Multiplan

Primary site of malignancy	IM IFNβ-1a use			Non-MS population controls			*P* value[a]	Odds ratio (95% CI)
	Malignancy (n)	Population (n)	%	Malignancy (n)	Population (n)	%		
Bladder	11	12892	0.09	16	25782	0.06	0.422	1.38 (0.64–2.96)
Brain	8	12892	0.06	13	25779	0.05	0.647	1.23 (0.51–2.97)
Colorectal	24	12888	0.19	29	25765	0.11	0.071	1.66 (0.96–2.84)
Esophageal	1	12894	0.01	4	25785	0.02	0.509	0.50 (0.06–4.47)
Hodgkin lymphoma	5	12890	0.04	11	25779	0.04	0.859	0.91 (0.32–2.62)
Kidney	8	12890	0.06	14	25778	0.05	0.765	1.14 (0.48–2.72)
Laryngeal	1	12893	0.01	4	25785	0.02	0.509	0.50 (0.06–4.47)
Leukemia	6	12890	0.05	10	25780	0.04	0.726	1.20 (0.44–3.30)
Lip/oral cavity	3	12892	0.02	8	25786	0.03	0.665	0.75 (0.20–2.83)
Liver	3	12894	0.02	6	25784	0.02	1.000	1.00 (0.25–4.00)
Lung	17	12892	0.13	44	25767	0.17	0.356	0.77 (0.44–1.35)
Melanoma	18	12883	0.14	31	25770	0.12	0.616	1.16 (0.65–2.08)
Multiple myeloma	3	12892	0.02	3	25783	0.01	0.401	2.00 (0.40–9.91)
Non-Hodgkin lymphoma	14	12890	0.11	30	25761	0.12	0.829	0.93 (0.49–1.76)
Pancreas	4	12893	0.03	4	25775	0.02	0.332	2.00 (0.50–8.00)
Pharyngeal/ nasopharyngeal	2	12893	0.02	4	25784	0.02	1.000	1.00 (0.18–5.46)
Stomach	2	12894	0.02	3	25783	0.01	0.755	1.33 (0.22–7.98)
Thyroid	19	12879	0.15	44	25755	0.17	0.589	0.86 (0.50–1.48)
Breast (females)	101	9922	1.02	178	19786	0.90	0.322	1.13 (0.89–1.45)
Cervix (females)	1	9962	0.01	19	19926	0.10	0.002	0.11 (0.01–0.79)
Ovary (females)	16	9964	0.16	22	19911	0.11	0.261	1.45 (0.76–2.77)
Uterine (females)	7	9962	0.07	22	19923	0.11	0.280	0.64 (0.27–1.49)
Prostate (males)	12	2923	0.41	24	5838	0.41	0.997	1.00 (0.50–2.00)
Testicular (males)	2	2927	0.07	3	5848	0.05	0.756	1.33 (0.22–7.98)

Note: [a]Due to correction for multiple comparisons (Bonferroni), statistical significance was achieved when $P < 0.002$.
Abbreviations: CI, confidence interval; IM IFNβ-1a, intramuscular interferon beta-1a; MS, multiple sclerosis.

Table 4 Malignancy in MS patients after IM IFNβ-1a use (n = 12,894) compared with MS patients with no IM IFNβ-1a use[a] (n = 25,788), i3 InVision Data Mart Multiplan

Primary site of malignancy	IM IFNβ-1a use			IM IFNβ-1a nonuse[a]			*P* value[b]	Odds ratio (95% CI)
	Malignancy (n)	Population (n)	%	Malignancy (n)	Population (n)	%		
Bladder	11	12892	0.09	27	25775	0.10	0.561	0.81 (0.40–1.64)
Brain	8	12892	0.06	42	25752	0.16	0.006	0.38 (0.18–0.81)
Colorectal	24	12888	0.19	33	25768	0.13	0.168	1.45 (0.86–2.46)
Esophageal	1	12894	0.01	3	25786	0.01	0.717	0.67 (0.07–6.41)
Hodgkin lymphoma	5	12890	0.04	10	25773	0.04	1.000	1.00 (0.34–2.93)
Kidney	8	12890	0.06	25	25779	0.10	0.255	0.64 (0.29–1.42)
Laryngeal	1	12893	0.01	1	25786	0.00	0.627	2.00 (0.13–31.98)
Leukemia	6	12890	0.05	24	25772	0.09	0.105	0.50 (0.20–1.22)
Lip/oral cavity	3	12892	0.02	7	25781	0.03	0.821	0.86 (0.22–3.31)
Liver	3	12894	0.02	5	25787	0.02	0.804	1.20 (0.29–5.02)
Lung	17	12892	0.13	48	25770	0.19	0.209	0.71 (0.41–1.23)
Melanoma	18	12883	0.14	48	25767	0.19	0.288	0.75 (0.44–1.29)
Multiple myeloma	3	12892	0.02	12	25778	0.05	0.252	0.50 (0.14–1.77)
Non-Hodgkin lymphoma	14	12890	0.11	28	25760	0.11	0.998	1.00 (0.53–1.90)
Pancreas	4	12893	0.03	5	25786	0.02	0.489	1.60 (0.43–5.96)
Pharyngeal/ nasopharyngeal	2	12893	0.02	7	25786	0.03	0.464	0.57 (0.12–2.75)
Stomach	2	12894	0.02	3	25788	0.01	0.755	1.33 (0.22–7.98)
Thyroid	19	12879	0.15	39	25765	0.15	0.927	0.97 (0.56–1.69)
Breast (females)	101	9922	1.02	174	19650	0.89	0.266	1.15 (0.90–1.47)
Cervix (females)	1	9962	0.01	9	19767	0.05	0.082	0.22 (0.03–1.74)
Ovary (females)	16	9964	0.16	24	19753	0.12	0.392	1.32 (0.70–2.49)
Uterine (females)	7	9962	0.07	17	19763	0.09	0.648	0.82 (0.34–1.97)
Prostate (males)	12	2923	0.41	36	5990	0.60	0.238	0.68 (0.35–1.31)
Testicular (males)	2	2927	0.07	1	6017	0.02	0.230	4.11 (0.37–45.38)

Notes: [a]IM IFNβ-1a nonuse is defined as no use of IM IFNβ-1a during a patient's time in the database; [b]Due to correction for multiple comparisons (Bonferroni), statistical significance was achieved when $P < 0.002$.

Abbreviations: CI, confidence interval; IM IFNβ-1a, intramuscular interferon beta-1a; MS, multiple sclerosis.

cancers, and cervical cancer. No overrepresentation of these cancers was observed. Findings from the intramuscular IFNβ-1a global safety database analysis were consistent with the results from the US claims data analysis. No significant differences in malignancy rates were observed between MS patients who used intramuscular IFNβ-1a and non-MS population controls, MS patients with no intramuscular IFNβ-1a use, or untreated MS patients.

We acknowledge the limitations of comparing malignancy reporting rates from the intramuscular IFNβ-1a global safety database with malignancy incidence rates. Reporting rates derived from spontaneous adverse drug reaction reporting in the intramuscular IFNβ-1a global safety database are associated with under-reporting. Under-reporting of latent events such as malignancy may be further amplified because the condition may not emerge until years later, making it less likely for the reporter to make an association easily between malignancy and any given therapeutic agent. In addition, the size of the exposed population can at best be estimated only roughly, based on a number of assumptions.

The intramuscular IFNβ-1a-treated population tends to consist predominantly of white females between 30 and 60 years of age (Biogen Idec, data on file). In the postmarketing surveillance evaluation, comparing postmarketing reports of malignancies with GLOBOCAN rates is limited by the fact that the intramuscular IFNβ-1a reporting rates were not standardized to a common age and gender distribution across GLOBOCAN regions. In addition, conclusions regarding the risk over time are limited due to the fact that the duration of intramuscular IFNβ-1a use in MS patients is unknown in this analysis. Given these limitations, postmarketing surveillance to evaluate changes in the nature of adverse drug reactions over time and to monitor for the emergence of unexpected adverse drug reactions not captured in trials with short treatment exposure is an essential component of pharmacovigilance.

A subanalysis of the claims data was performed to prevent prior immunosuppressive use from potentially confounding the calculated risk of developing malignancies. Malignancy was compared between subjects in the intramuscular IFNβ-1a use group with no history of immunosuppressive

Table 5 Malignancy in MS patients after IM IFNβ-1a use (n = 12,894) compared with untreated MS patients[a] (n = 12,894), i3 InVision Data Mart Multiplan

Primary site of malignancy	IM IFNβ-1a use			Untreated MS[a]			*P* value[b]	Odds ratio (95% CI)
	Malignancy (n)	Population (n)	%	Malignancy (n)	Population (n)	%		
Bladder	11	12,892	0.09	8	12,888	0.06	0.491	1.37 (0.55–3.42)
Brain	8	12,892	0.06	22	12,865	0.17	0.009	0.36 (0.16–0.81)
Colorectal	24	12,888	0.19	22	12,882	0.17	0.769	1.09 (0.61–1.95)
Esophageal	1	12,894	0.01	1	12,893	0.01	1.000	1.00 (0.06–15.99)
Hodgkin lymphoma	5	12,890	0.04	3	12,887	0.02	0.477	1.67 (0.40–6.97)
Kidney	8	12,890	0.06	7	12,887	0.05	0.796	1.14 (0.41–3.15)
Laryngeal	1	12,893	0.01	1	12,893	0.01	1.000	1.00 (0.06–15.99)
Leukemia	6	12,890	0.05	8	12,884	0.06	0.592	0.75 (0.26–2.16)
Lip/oral cavity	3	12,892	0.02	4	12,890	0.03	0.705	0.75 (0.17–3.35)
Liver	3	12,894	0.02	3	12,893	0.02	1.000	1.00 (0.20–4.96)
Lung	17	12,892	0.13	18	12,876	0.14	0.863	0.94 (0.48–1.83)
Melanoma	18	12,883	0.14	21	12,879	0.16	0.630	0.86 (0.46–1.61)
Multiple myeloma	3	12,892	0.02	3	12,882	0.02	0.999	1.00 (0.20–4.95)
Non-Hodgkin lymphoma	14	12,890	0.11	16	12,878	0.12	0.713	0.87 (0.43–1.79)
Pancreas	4	12,893	0.03	2	12,892	0.02	0.410	2.00 (0.37–10.92)
Pharyngeal/ nasopharyngeal	2	12,893	0.02	4	12,891	0.03	0.410	0.50 (0.09–2.73)
Stomach	2	12,894	0.02	2	12,891	0.02	1.000	1.00 (0.14–7.10)
Thyroid	19	12,879	0.15	18	12,874	0.14	0.870	1.06 (0.55–2.01)
Breast (females)	101	9922	1.02	87	9884	0.88	0.317	1.16 (0.87–1.54)
Cervix (females)	1	9962	0.01	5	9953	0.05	0.088	0.20 (0.02–0.71)
Ovary (females)	16	9964	0.16	13	9946	0.13	0.580	1.23 (0.59–2.56)
Uterine (females)	7	9962	0.07	12	9951	0.12	0.247	0.58 (0.23–1.48)
Prostate (males)	12	2923	0.41	17	2926	0.58	0.352	0.71 (0.34–1.48)
Testicular (males)	2	2927	0.07	0	2939	n/a	n/a	n/a

Notes: [a]Untreated MS defined as no use of an indicated MS treatment and no immunosuppressive treatment at any time in the database; [b]Due to correction for multiple comparisons (Bonferroni), statistical significance was achieved at $P < 0.002$.

Abbreviations: CI, confidence interval; IM IFNβ-1a, intramuscular interferon beta-1a; MS, multiple sclerosis; n/a, not applicable.

use and subjects in the untreated MS group. Subjects with a malignancy in the intramuscular IFNβ-1a use/no immunosuppressive use group were excluded if they had at least two ICD-9 codes for the malignancy prior to the first intramuscular IFNβ-1a prescription date. No increased risk of malignancy was observed in the intramuscular IFNβ-1a use/no immunosuppressive use group compared with the untreated MS group. Although a subset of malignancies may not have been captured, since excluding patients with immunosuppressive use removed cancers treated with immunosuppressive drugs from both groups, the comparison of risk between the two groups is nevertheless valid.

Though insurance claims data provide observational data powered with large numbers, analyses based on these data have inherent limitations. To control for potential confounders within the claims database analysis, patients were matched to population controls for age, gender, and follow-up time, and frequency matching based on age was performed for the case-to-case comparisons. This evaluation did not control for possible cancer risk factors such as diet, environmental exposures, family history, smoking status, and prior and/or concomitant medication use (except for immunosuppressive use). In addition, selection bias may have been introduced, as an insurance claims database captures only those individuals or family members who carry medical insurance. It is difficult to know if and to what extent these uncontrolled factors influenced the results, but each group analyzed would be similarly biased.

Some patients identified in this analysis as intramuscular IFNβ-1a nonusers may have previously used intramuscular IFNβ-1a; similarly, patients identified as intramuscular IFNβ-1a users may have received other MS therapies or immunosuppressive prior to initiating treatment with intramuscular IFNβ-1a and prior to entering the database. It is not uncommon for an individual to move in and out of different insurance plans over time, resulting in treatment information for the time before and/or after the individual was in an included plan being omitted from the insurance claims database. Information would also be missing from the database if patients paid out of pocket for pharmacy expenses, though few MS patients are likely to do so. As a result, it is not possible to eliminate bias or confounding

within a retrospective claims data analysis fully, a limitation that is not differentiated by treatment group.

Like any electronic medical database, this database may have included coding inaccuracies. However, the capture of inaccurate data was limited by the requirement of at least two diagnosis codes for each malignancy. In addition, any inaccuracies resulting from coding errors should be equally represented between the intramuscular IFNβ-1a use group and each comparison group. Finally, considering that cancers may take years to develop, we acknowledge that the short follow-up time of 3 years restricts the conclusions that can be drawn from this analysis.

Despite the limitations of an insurance claims dataset, it provides the strength of a large reference population with a known denominator and permits the evaluation of various treatment exposures in cohorts of patients with MS as well as a non-MS control population. In addition, the longitudinal nature of a claims database captures continuous service dates rather than the individual assessments traditionally performed in cohort studies, allowing for an evaluation of the timing of events.[21]

This study assessed the risk of malignancy in patients using intramuscular IFNβ-1a for the treatment of MS. Evaluating two data sources, postmarketing surveillance, and US claims data, we found no evidence of an increased risk of cancer with the use of intramuscular IFNβ-1a.

With intramuscular IFNβ-1a, as with all drugs, the risks and benefits of the therapy must be considered when selecting treatments for individual patients. The complexity of making appropriate treatment decisions in MS increases as more options for treatment, each with a unique safety profile, become available. For many of the newer therapies, long-term safety has yet to be determined. This evaluation provides valuable information about the risk of malignancy with intramuscular IFNβ-1a based on 15 years of real-world experience and supports the safety profile previously established through the intramuscular IFNβ-1a development program and pivotal trials.

Disclosure

Anne Dilley of Biogen Idec Inc assisted with the methodology development, and Susan Friend of Biogen Idec Inc assisted in compiling the intramuscular IFNβ-1a safety data used in this paper.

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References

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372:1502–1517.
2. Kingwell E, Tremlett H. Interferons and multiple sclerosis: is it plausible that beta-IFN treatment could influence the risk of cancer among MS patients? *Expert Rev Neurother*. 2009;9:1263–1265.
3. Ottenhoff TH. Selective modulation of T-cell responses in autoimmunity and cancer. *Immunol Today*. 1996;17:54–55.
4. Achiron A, Barak Y, Gail M, et al. Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments. *Breast Cancer Res Treat*. 2005;89:265–270.
5. Bahmanyar S, Montgomery SM, Hillert J, Ekbom A, Olsson T. Cancer risk among patients with multiple sclerosis and their parents. *Neurology*. 2009;72:1170–1177.
6. Palo J, Duchesne J, Wikstrom J. Malignant diseases among patients with multiple sclerosis. *J Neurol*. 1977;216:217–222.
7. Møller H, Kneller RW, Boice JD Jr, Olsen JH. Cancer incidence following hospitalization for multiple sclerosis in Denmark. *Acta Neurol Scand*. 1991;84:214–220.
8. Midgard R, Glattre E, Grønning M, Riise T, Edland A, Nyland H. Multiple sclerosis and cancer in Norway: a retrospective cohort study. *Acta Neurol Scand*. 1996;93:411–415.
9. Koch-Henriksen N. The Danish Multiple Sclerosis Registry: a 50-year follow-up. *Mult Scler*. 1999;5:293–296.
10. Sumelahti ML, Pukkala E, Hakama M. Cancer incidence in multiple sclerosis: a 35-year follow-up. *Neuroepidemiology*. 2004;23:224–227.
11. Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. *Int J Cancer*. 2006;118:979–984.
12. Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ. Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. *J Neurol Neurosurg Psychiatry*. 2010;81:215–221.
13. Handel AE, Ramagopalan SV. Multiple sclerosis and risk of cancer: a meta-analysis. *J Neurol Neurosurg Psychiatry*. 2010;81:1413–1414.
14. Lebrun C, Debouverie M, Vermersch P, et al. Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. *Mult Scler*. 2008;14:399–405.
15. Sandberg-Wollheim M, Kornmann G, Bischof D, et al. The risk of malignancy is not increased in patients with multiple sclerosis treated with subcutaneous interferon beta-1a: analysis of data from clinical trial and post-marketing surveillance settings. *Mult Scler*. 2011;17:431–440.
16. Lebrun C, Vermersch P, Brassat D, et al. Cancer and multiple sclerosis in the era of disease-modifying treatments. *J Neurol*. 2011;258:1304–1311.
17. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol*. 1996;39:285–294.
18. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med*. 2000;343:898–904.
19. Maintenance and Support Services Organization. Medical Dictionary for Regulatory Activities (MedDRA). Available from: http://www.meddramsso.com. Accessed April 24, 2012.
20. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer incidence and mortality worldwide: IARC CancerBase no 10. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr. Accessed November 8, 2011.
21. Stürmer T, Funk MJ, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. *Epidemiology*. 2011;22:298–301.