Natalizumab-associated melanoma: A Report of 139 cases from the Southern Network on Adverse Reactions (SONAR)

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ABSTRACT

Natalizumab is an effective immunosuppressive therapy for multiple sclerosis that received its initial FDA approval in 2004. Its most notable toxicity is progressive multifocal leukoencephalopathy (PML), an opportunistic infection that is the focus of an FDA mandated Registry (the Tysabri Outreach Commitment to Health (TOUCH) Outcomes Registry. The Southern Network on Adverse Reactions identified a fatal case of Natalizumab associated urethral melanoma and undertook an extensive evaluation of all cases of Natalizumab-associated melanoma included in the FDA's Adverse Event Reporting System (FAERS) (between 2005 and 2014). Characteristics of these patients and report quality were analyzed. Report quality was based on a 15 point scale of various components. The mean patient age at the time of diagnosis of melanoma was 46 (s.d. 11). Seventeen patients were diagnosed with cutaneous melanoma developing in non-sun-exposed areas. We found that cases reported through the TOUCH registry were of lower quality (mean score 7.7) compared to others that reported outside of the USA (mean score 8.5, p<.008). Our findings suggest that in the United States, the TOUCH Registry should be expanded to require clinicians to report details of Natalizumab-associated melanoma, an opportunistic illness that frequently develops in immunocompromised persons. Also, the FDA-approved product label for Natalizumab should be revised to include information on occurrences of melanoma among Natalizumab-treated MS patients, particularly those who have cutaneous nevi prior to Natalizumab initiation. Natalizumab-treated MS patients and their physicians should be vigilant for changes in nevi appearances and development of new cutaneous lesions (particularly in non-sun-exposed cutaneous areas).

BACKGROUND

- Melanoma is the most dangerous form of skin cancer and affected over 76,000 people in 2014[1]
- There are 3 types of melanoma: cutaneous, mucosal and ocular
  - Cutaneous is the most common melanoma[2]
- Natalizumab (Tysabri) is a monoclonal antibody designed to block α4 integrins and is given to Multiple Sclerosis (MS) patients[3]
- Progressive Multifocal Leukoencephalopathy (PML) is a serious and generally fatal infection of the central nervous system caused by the John Cunningham (JC) virus in immunocompromised patients[4]
- 3 fatal cases of PML were identified after the 2004 FDA approval causing the drug to be voluntarily removed from the United States market in 2005[5]
- In 2006 Natalizumab was put back on the Untied States market with a Risk Management program, Tysabri Outreach Commitment to Health (TOUCH), in place[6]
  - Anyone in the United States who is prescribed Natalizumab must be registered with the TOUCH program
  - TOUCH is designed to catch early cases of PML and opportunistic infections
- A SONAR investigator identified a 34 year old female with urethral melanoma shortly after Natalizumab administration in 2014
- SONAR undertook a comprehensive investigation to follow up on this safety concern and evaluated all FDA reported cases of melanoma and Natalizumab
- Focus of the investigation is the characterization of these patients and the completeness and quality of the reports

OBJECTIVES

1) To characterize Natalizumab treated patients who developed melanoma
2) To determine the completeness and quality of reports
3) To determine the differences between cases reported through the TOUCH system and those that did not

METHODS

Data Source

- FDA Adverse Events Reports and Medwatch Reports
- Patient , treatment, outcome and melanoma characteristics were taken from the reports and put into a dataset for analysis

Classification of Melanoma

- Site
  - defined as cutaneous, mucosal or ocular
- Sun exposure
  - defined by primary site location and if it is exposed to the sun using scales from previous work [7,8]

Quality Score

- A 15 point quality score was developed for individual cases
  - Demographics
    - 4 points total
    - If age, race, gender and country were given
  - Pharmacy
    - 3 points total
    - If Natalizumab start date, duration of treatment and melanoma treatment were given
  - Clinical
    - 8 points total
    - If melanoma site, lymph node status, Breslow depth, pre-existing nevi, family history of melanoma, prior immunosuppressive treatment given, survival and start date of melanoma were given

TOUCH Reporting Indication

- **United States Cases**
  - **Heavy TOUCH (case reported through the TOUCH system)**
  - **Light TOUCH (case reported outside the TOUCH system but used information from TOUCH)**
  - **No TOUCH (case reported outside the TOUCH system and no information from the TOUCH registry was used)**
- **Outside the United States**
  - **No TOUCH**

Analysis

- Descriptive statistics for characteristics of patients
- Statistically significant pair-wise comparisons between TOUCH groups (generalized p<0.05) were identified using Univariate Optimal Discriminant Analysis1(UniODA) and are presented for every attribute (column 1). For each unique application UniODA identifies the model (column 3) that predicts observations' actual class membership (column 2) with maximum accuracy normed against chance. This is accomplished by explicitly maximizing (optimizing) the effect strength for sensitivity (ESS) statistic: for each unique application, ESS=0 is the level of classification accuracy expected by chance, and ESS=100 is perfect, errorless classification. ESS is a measure of how accurately the model classifies observations' actual class category status across the sample, and it is invariant over base rate. While the ESS and the effect strength for predictive value (ESP) statistics are normed in the same manner, ESP is a measure of how accurately the model makes point predictions regarding the class membership status of individual observations, and it varies as a function of base rate. Monte Carlo simulation using Fisher's randomization algorithm is used to estimate the exact Type I error rate.[9]

RESULTS

	Total	US	Non-US
	N=139	N=97 (70%)	N=42 (30%)
Quality Score			
Total [median (Q1, Q3)] max=15	8.5 (7, 10)	8.5 (7, 10)	8.5 (7.5, 9.5)
Clinical [median (Q1, Q3)] max=8	3 (2.5, 4.5)	3 (2.5, 4.5)	3.5 (2.5, 4)
Pharmacy [median (Q1, Q3)] max=3	2.5 (2, 3)	2.5 (2, 3)	2.5 (2, 3)
Demographics [median (Q1, Q3)] max=4	3 (3, 3)	3 (3, 3)	3 (3, 3)
Age (median [range])*	46 [21, 74]	47 [21, 74]	39 [21, 63]
Number of updates (median)*	2	2	1
Number of months of information from melanoma diagnosis (median)	5	5	5
Gender N (%)			
Male	31 (22)	22 (23)	9 (21)
Female	108 (78)	75 (77)	33 (79)
Disease Natalizumab prescribed N(%)			
Multiple Sclerosis	137 (98)	95 (98)	42 (100)
Crohns	1 (1)	1 (1)	0
Not Known	1 (1)	1 (1)	0
Melanoma Site N (%)			
Cutaneous	106 (76)	75 (77)	31 (74)
Mucosal	2 (1)	2 (2)	0
Ocular	5 (4)	3 (3)	2 (5)
Not Known	26 (19)	17 (18)	9 (21)
Site Sun Exposed N (%)			
Yes	88 (63)	63 (65)	25 (60)
No	25 (18)	18 (19)	7 (17)
Not Known	26 (19)	16 (16)	10 (24)
Time on drug until Melanoma Diagnosis N (%)*			
0-24 months	44 (32)	33 (34)	11 (26)
25-48 months	23 (17)	11 (11)	12 (29)
49-72 months	10 (7)	4 (4)	6 (14)
73-96 months	2 (1)	2 (2)	0
not specified	60 (43)	47 (49)	13 (31)
Alive at follow up N (%)	130 (94)	90 (93)	40 (95)
Concomitant drug use N (%)	51 (37)	32 (33)	19 (45)
Melanoma Treatment N (%)			
Chemotherapy	2 (1)	2 (2)	0
Chemotherapy and radiation	1 (1)	1 (1)	0
Surgery	92 (66)	63 (65)	29 (69)
Radiation	1 (1)	0	1 (2)
Surgery combination	9 (6)	9 (9)	0
Other	3 (2)	2 (2)	1 (2)
no	1 (1)	0	1 (2)
Not applicable	19 (14)	12 (12)	7 (17)
Unknown	11 (8)	8 (8)	3 (7)
TOUCH N(%)			
Heavy	N/A	20 (20)	0
Light	N/A	54 (56)	0
None	N/A	23 (24)	42 (100)
Nevi history N (%)			
Yes	25 (18)	16 (16)	9 (21)
No	40 (29)	24 (25)	16 (38)
Unknown	74 (53)	57 (59)	17 (41)
Change in Nevi N (%)			
Yes	22 (16)	14 (14)	8 (19)
No	117 (84)	83 (86)	34 (81)
Reporter N (%)*			
Neurologist	40 (29)	28 (29)	12 (29)
Unknown	23 (17)	9 (9)	14 (33)
Patient	19 (14)	19 (20)	0
Nurse	17 (12)	16 (17)	1 (2)
Physician	10 (7)	3 (3)	7 (17)
Family	5 (4)	5 (5)	0
Registered Nurse	5(4)	5 (5)	0
Investigator	6 (4)	1 (1)	5 (12)
Physician Assistant	2 (1)	2 (2)	0
ANSM	2 (1)	0	2 (5)
Health Care Professional	2 (1)	2 (2)	0
Consumer	2 (1)	2 (2)	0
Doctor	1 (1)	1 (1)	0
Manufacturer Report	1 (1)	1 (1)	0
Other Authority	1 (1)	0	1 (2)
Assistant	1 (1)	1 (1)	0
Infusion Nurse	1 (1)	1 (1)	0
Nurse Practitioner	1 (1)	1 (1)	0

Table 1: Characteristics of Natalizumab treated melanoma population: * indicates statistically significant difference between USA and Non-USA group

Variable	TOUCH Group Comparison	Predict Indicated TOUCH Group if	N	% Accurately Identified	ESS	% Correct Predictions	ESP
Melanoma Site*	Heavy TOUCH	Site =0	20	40	35.4	88.9	52.5
	No TOUCH USA	Site >0	22	95.4		63.6	
	Heavy TOUCH	Site =0	20	40	27	53.3	33
	Light TOUCH	Site >0	54	87		79.7	
Family History of Melanoma*	Heavy TOUCH	History =0	20	100	21.7	52.6	52.6
	No TOUCH USA	History > 0	23	21.7		100	
	Heavy TOUCH	History = 0	20	100	24.1	32.8	32.8
	Light TOUCH	History > 0	54	24.1		100	
	Heavy TOUCH	History ≤ 0.5	20	100	23.8	38.5	38.3
	No TOUCH Non-USA	History = 1	42	23.8		100	
Pre-Existing Nevi (PEN)*	Heavy TOUCH	PEN ≤ 0.25	20	90	27	34.6	25.5
	Light TOUCH	PEN > 0.25	54	37		90.9	
	Heavy TOUCH	PEN ≤ 0.25	20	90	26.4	39.1	28
	No TOUCH Non-USA	PEN > 0.25	44	36.4		88.9	
Clinical Score*	Heavy TOUCH	Clinical Score ≤ 2.5	20	50	31.5	50	31.5
	Light TOUCH	Clinical Score > 2.5	54	81.5		81.5	
	Heavy TOUCH	Clinical Score ≤ 2.75	20	70	39	51.9	34.8
	No TOUCH Non-USA	Clinical Score > 2.75	42	69		82.9	
Number of Updates*	Heavy TOUCH	Updates > 1	20	75	32.1	45.4	28.2
	No TOUCH Non-USA	Updates < 1	42	57.1		82.8	
	Light TOUCH	Updates > 1	54	79.6	36.8	70.5	39.1
	No TOUCH Non-USA	Updates < 1	42	57.1		68.6	
Age*	Light TOUCH	Age > 39	50	76	27.4	67.9	28.4
	No TOUCH Non-USA	Age < 39	37	51.4		61.3	
	No TOUCH USA	Age > 40	22	90.9	45	54.1	45
	No TOUCH Non-USA	Age < 40	37	54.1		90.9	
Months of Information*	Light TOUCH	Months > 0	54	94.4	25.4	63.8	45
	No TOUCH Non-USA	Months = 0	42	31		81.2	

Table 2: Bivariate TOUCH-Category UniODA Comparisons: * indicates statistical significance

Sun Exposure	United States N(%)	Non-United States N(%)	Total
yes	63 (84)	25 (81)	88 (83)
no	12 (16)	5 (16)	17 (16)
unknown	0	1 (3)**	1(1)**

** source is unconfirmed skin for metastasis to the liver

Table 3: Distribution of sun exposed and non sun exposed cutaneous sites

CONCLUSIONS

- **The FDA reports are of poor quality with less than half (median of 3 out of 8) of relevant information not included for clinical data**
- **Heavy TOUCH (USA, reported through TOUCH, N=20) cases tend to have lower clinical quality scores compared to Light TOUCH (USA, used TOUCH information, N=54) and No TOUCH (USA ,N=23; Non-USA, N=42) cases**
  - **Melanoma site and relevant medical history stand out as being neglected in Heavy TOUCH reports**
- High percent of cutaneous melanoma in non sun exposed sites
  - As α4 integrin has been reported to inhibit both immune cells and prevent the movement of melanoma cells, its suppression by Natalizumab is a putative cause of what we suspect is a anomalous percentage of melanomas in this population[10].

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