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

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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 database 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 1

Quality Score:
- A 15 point quality score was developed for individual demographics
- 4 points total
- If age, race, gender and country were given
- 2 points total
- If Natalizumab start date, duration of treatment and melanoma treatment were given
- 8 points total
- If melanoma site, lymph node status, Br-slew depth, pre-existing nevi, family history of melanoma, prior immunosuppressive treatment, duration 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

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 Analysis (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

RESULTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>TOUCH Group Comparison</th>
<th>Predict Indicator</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma Site*</td>
<td>Heavy TOUCH</td>
<td>Site = 10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>No TOUCH</td>
<td>Site = 10</td>
<td>77</td>
</tr>
<tr>
<td>Age &lt; 39</td>
<td>Yes</td>
<td>Age &lt; 39 = 1</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Age &lt; 39 = 0</td>
<td>44</td>
</tr>
<tr>
<td>History &gt; 0</td>
<td>Yes</td>
<td>History &gt; 0 = 1</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>History &gt; 0 = 0</td>
<td>60</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Yes</td>
<td>Nevirapine = 1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Nevirapine = 0</td>
<td>80</td>
</tr>
<tr>
<td>Age (median (Q1, Q3))</td>
<td>33 (22)</td>
<td>Age (median (Q1, Q3)) = 33</td>
<td>100</td>
</tr>
<tr>
<td>Total (median (Q1, Q3))</td>
<td>34.8 (25.4, 47.2)</td>
<td>Total (median (Q1, Q3)) = 34.8</td>
<td>100</td>
</tr>
<tr>
<td>Light TOUCH</td>
<td>Yes</td>
<td>Light TOUCH = 1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Light TOUCH = 0</td>
<td>100</td>
</tr>
<tr>
<td>Age (median (Q1, Q3))</td>
<td>25.4 (22.1, 30.5)</td>
<td>Age (median (Q1, Q3)) = 25.4</td>
<td>100</td>
</tr>
<tr>
<td>Total (median (Q1, Q3))</td>
<td>32.4 (25.3, 40.5)</td>
<td>Total (median (Q1, Q3)) = 32.4</td>
<td>100</td>
</tr>
<tr>
<td>Light TOUCH</td>
<td>Yes</td>
<td>Light TOUCH = 1</td>
<td>100</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
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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 quality scores compared to Light TOUCH (USA, used TOUCH information, N=54) and No TOUCH (USA, N=22, N=4, No TOUCH USA, N=22, N=4) cases
- Melanoma site and relevant medical history stand out as being neglected in Heavy TOUCH reports

REFERENCES

- Novox, Virginia; Sartor, Oliver; Bennett, Charles. University of South Carolina College of Pharmacy.
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BACKGROUND

- Melanoma is the most dangerous form of skin cancer and affected over 76,000 people in 2014.
- There are 3 types of melanoma: cutaneous, mucosal and ocular.
- Cutaneous is the most common melanoma.
- Natalizumab (Tysabri) is a monoclonal antibody designed to block a molecule of Integrins and is given to Multiple Sclerosis (MS) patients.
- Proactive Multifocal Leukocapillaryopathy (MPL) is a serious and generally fatal infection of the central nervous system caused by the John Cunningham (UC) virus in immunocompromised patients.
- 3 fatal cases of PM were identified after the 2004 FDA approval causing the drug to be voluntarily removed from the United States market in 2005.
- In 2008, Tysabri was put back on the United States market with a Risk Management program, Tysabri Outreach Commitment to Health (TOUCH), in place.
- Anyone in the United States who is prescribed Natalizumab must be registered with the TOUCH program.
- TOUCH is designed to catch early cases of PM and make sure it is reported.
- A SONAR investigator identified 34 year old female with urethral melanoma shortly after Natalizumab was prescribed.
- Focus of the investigation is the characterization of these patients and the completeness and quality of the reports.