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CASE REPORT

Association of melanoma and natalizumab therapy in the Italian MS population: a second case report

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Abstract There is debate about a possible association between natalizumab treatment and higher risk of melanoma. Here we report a case of melanoma in a patient who developed melanoma after 77 infusions of natalizumab, without known risk factors. Pharmacovigilance programs of new drugs can help to monitor adverse events in patients at risk.

Keywords Multiple sclerosis · Natalizumab · Melanoma

Case report

We report a case of melanoma during treatment with natalizumab (Tysabri®, Biogen-Idec), a humanized monoclonal antibody against the α_4 subunit of integrins, approved for the treatment of multiple sclerosis (MS). A 38-year-old lady, without familiar history of melanoma or atypical naevi, previously treated with interferon β1a (Avonex®, Biogen-Idec) for 4 years, was enrolled in the SENTINEL trial in May 2002. She received natalizumab for 30 monthly infusions in association with Avonex® administered intramuscularly once a week and, subsequently, during the follow-up trial, five infusions with natalizumab alone until February 2006. On July 2006, she was enrolled in the STRATA study, an extension study on long-term safety of Tysabri. On January 2007, she noticed a pigmented, not painful mole in her left foot plant. She underwent dermatology assessment every 6 months, until excision was decided on October 2009 as a routine diagnostic procedure, when she had received 77 infusions of natalizumab in total. Histological analysis resulted in a malignant melanoma (Clark level III, Breslow index 0.5 mm). No evidence of metastasis was found after stadiation with physical exam, upper abdomen ultrasound scan, popliteal and inguinal lymph nodes ultrasound scan and chest radiography. After stopping Tysabri, she started treatment with glatiramer acetate (Copaxone®, Sanofi-Aventis) on January 2010.

This is the sixth reported case of melanoma in natalizumab-treated patients [1–4]. A causal relationship between natalizumab treatment and melanoma has not been proven [5]. Melanoma has been reported in patients with MS [6] and rheumatoid arthritis [7] treated with other biological therapies.

Blockade of α_4 integrins on leukocytes might impair anti-tumour surveillance. The heterodimer $\alpha_4\beta_1$ can be expressed by melanoma cells, although it is not clear whether it promotes [8] or prevents tumor spreading [9, 10].

As per September 2009, 74,800 person-years (py) have been treated with natalizumab (courtesy of Biogen-Dompé, Italy), the worldwide incidence of melanoma being 8 cases/100,000 py, still lower than age-adjusted incidence rate (IR) in the US general population [19.6/100,000 py (http://www.seer.cancer.gov/statfacts/html/melan.html; accessed 09/02/2010)].

It is noteworthy that this is the second reported melanoma case among natalizumab-treated individuals in Italy, where the age-adjusted IR is about 16 cases/100,000 py [11]. We estimated the py number for individuals treated with natalizumab in Italy as about 2,900 (source: registry of Tysabri, Italian drug regulatory agency, AIFA). Thus,

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an estimate of the incidence of melanoma in the MS population treated with natalizumab could be higher (69/100,000 py) than expected [11].

Discussion and conclusion

The role of blockade of the α_4 integrin in melanoma pathogenesis requires further investigations. The limited number of reports about the association of Tysabri treatment and melanoma might not exclude natalizumab therapy to MS patients with familiar history of melanoma or atypical naevi. Only one out of the six reported cases had familial history of melanoma [2] and two were reported to have atypical naevi [3, 4], while one had previous history of melanoma [1]. However, it should be considered instructing patients about reporting skin lesions and recommending dermatological assessments before, during and after natalizumab treatment, as well as inclusion in the program of country surveillance.

Conflict of interest AL received honoraria for consultation, speaking or both at meeting for Merck-Serono and Biogen-Idec. AU received financial support for research, honoraria for consultation, speaking or both at meeting for Genetech, Roche, Allergan, Merck-Serono, Sanofi-Aventis. GM received financial support for research, honoraria for consultation, speaking or both at meeting for Bayer-Schering, Biogen-Idec, Sanofi-Aventis and Merck-Serono. MB and EC do not report conflicts of interest.

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