Therapy of multiple sclerosis (MS) with disease-modifying agents such as natalizumab or fingolimod has been clinically associated with the development of cutaneous melanoma.

Published data do not support the hypothesis of a direct action of natalizumab or fingolimod on melanoma cell proliferation and migration that could lead to tumor progression. More probably, by acting on the tumor microenvironment through changing in the tumor inflammatory cell infiltration and angiogenesis, these treatments could indirectly favor melanoma evolution.

Recent innovations in disease treatment markedly improved expectancy for multiple sclerosis (MS) patients, reducing their disability burden and improving the quality of life. In fact, several drugs are now available able to modify the pathology course, limiting both relapses and disease progression [1]. However, a careful balance between benefits and risks must be done on individual basis since the more effective treatments often cause themselves severe adverse effects.

Natalizumab (Tysabri) and fingolimod (FTY720, Gilenya), are among the most effective and diffuse therapies for patients with MS. Natalizumab is a humanized monoclonal antibody directed against the α4 integrin subunit that is expressed on T and B lymphocytes, monocytes, macrophages, natural killer (NK) and dendritic cells. By blocking α4 integrin, natalizumab interferes with immune cell migration across the blood brain barrier inhibiting trans-endothelial migration to the central nervous system [2]. Natalizumab shows important anti-inflammatory responses and neuroprotective effects, but it enhances the risk of developing a rare brain infection, the progressive multifocal leukoencephalopathy. Other side effects include hepatotoxicity, allergic reactions and a higher risk of infection [2].

Fingolimod is a non-specific small molecule acting as a sphingosine-1-phosphate receptor modulator, causing receptor internalization and leading to a redistribution of circulating lymphocytes into secondary lymphoid organs thereby inducing a state of peripheral lymphopenia. Thus, fingolimod reduces infiltration of autoreactive lymphocytes into the central nervous system [3]. The sphingosine-1-phosphate receptor is a potent inducer of endothelial cell chemotaxis and phosphorylated fingolimod, acting as a receptor agonist, induces endothelial cell migration, adherens junction assembly and inhibits vascular endothelial growth factor (VEGF)-A-mediated vascular permeability [4]. Fingolimod-mediated loss of sphingosine-1-phosphate receptor from the astrocytes attenuates neuroinflammation, demyelination and axonal damage [5]. However, fingolimod treatment in MS has been linked to herpetic infections, cardiac and hepatic adverse effects [6].

There are reports in the literature about the development of cutaneous melanoma following MS therapy with either natalizumab [7-13,15-18] or fingolimod [14,19-22] but the number of cases was low and did not reach any statistical significance. Therefore, melanoma occurrence in these patients could be merely a coincidence [20]. Nevertheless, recent studies indicated a statistically significant association of melanoma occurrence with the treatment with those disease modifying drugs [21-22]. Prospective follow-up of MS patients treated with natalizumab evaluated possible modifications of naevi under treatment and found out that either after 14 months [23] or after 4 years [24] the degree of clinical and dermoscopic changes during natalizumab therapy did not differ from the rate of spontaneous evolution of naevi in untreated individuals as reported in the literature. These data suggest that inhibition of α4β1 integrin does not directly promote malignant transformation of melanocytes.

Fingolimod behaves as an antiangiogenic drug [25] and inhibits tumor growth and metastatic spreading in vivo in murine melanoma and breast cancer models [26]. Moreover, fingolimod induces apoptosis in vitro in mouse melanoma cells and blocks metastasis spreading both in a syngeneic mouse model [27] or in canine melanoma [28]. However, a protumorigenic role of fingolimod was also proposed, with this drug acting by enhancing accumulation of myeloid-derived suppressor cells (MDSCs) around the tumor lesion [28].

Natalizumab could affect melanoma progression through different mechanisms. When the α4 integrin subunit was
introduced into a murine melanoma cell line, its expression significantly reduced the melanoma invasive potential both in vitro in a Matrigel assay and in vivo in a melanoma mouse model. Thus, natalizumab-mediated blockage of the α4 integrin could prompt the invasive stage of metastasis formation. Conversely, other reports indicated that α4β1 integrin is frequently over-expressed in highly invasive melanoma cells and integrin inhibition could prevent metastasis spreading. In addition, in vitro prolonged treatment of human NK cells, which express the α4β1 integrin, resulted into impaired NK cell degranulation towards melanoma cells. Similarly, NK cell migration in the direction of melanoma cells was significantly reduced in the presence of natalizumab. Finally, α4β1 integrin expression was diminished by natalizumab treatment in vitro as well as in MS patients, decreasing with time of natalizumab therapy, suggesting that this drug could alter NK-mediated immune surveillance against melanoma with a protumorgenic outcome.

Therefore, natalizumab and fingolimod can act either as aprotumorogenic or as antitumorogenic molecules. Therefore, a conclusion on the relationship between these drugs and melanoma has not been drawn yet.

Our in vitro data indicate that in general neither fingolimod nor natalizumab directly act on melanoma cells to prompt proliferation or invasion but have instead an antitumorogenic action. A possible indirect action could be rather executed by fingolimod through induction of VEGF-A expression and recruitment of immune-suppressive MDSCs and by natalizumab through impairment of NK cell functions. Therefore, treatment with these drugs can modify tumor microenvironment towards an immune-suppressive, proangiogenic one, favoring melanoma progression.

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Keywords

Multiple sclerosis, melanoma, microenvironment

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