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REVIEW

Immunomodulatory drugs (natalizumab), worsening of multiple sclerosis, rebound effect and similitude

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Background: **Homeopathic treatment is based on the principle of similitude ('like cures like') administering to sick individuals substances that cause similar symptoms in healthy individuals, employing the paradoxical or biphasic action of the organism as therapeutic response. This homeostatic, vital or secondary action of the organism is scientifically explained by the rebound effect of drugs, resulting in worsening of symptoms after enantiopathic treatment withdrawal. Natalizumab reduces relapses in patients with active multiple sclerosis (MS), but recent studies report severe worsening of MS after suspension of treatment, as a consequence of the rebound effect.**
Method: **Extending this source of evidence, this work reviews research that demonstrates secondary worsening of MS after discontinuation of natalizumab, a human monoclonal antibody that suppresses the disease inflammatory activity as primary action.**
Results: **Several studies refer to the immune reconstitution inflammatory syndrome (IRIS) as a plausible explanation of reactivation of MS after withdrawal of natalizumab: a rebound effect or secondary action of the organism in response to the primary immunosuppression caused by the drug.**
Conclusion: **Relapses of MS after discontinuation of natalizumab treatment indicate rebound of disease activity, supporting the homeopathic principle and warning healthcare professionals about this serious iatrogenic event.** *Homeopathy* (2013) **102**, 215–224.

Keywords: Homeopathy; Law of similars; Pharmacodynamic action of homeopathic remedy; Rebound effect; Paradoxical reaction; Natalizumab; Multiple sclerosis; Immune reconstitution inflammatory syndrome

Introduction

The pharmacodynamic action of homeopathic medicine or principle of similitude ('like cures like') is based on the 'primary action of the drug followed by secondary and opposite action of the organism', described many times in various classes of drugs[1,2]:

"Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counter-action*" (*Organon*, paragraph 63).

Proposing to employ such 'secondary action' in a curative way, Hahnemann suggested use medicines that in their 'primary action' elicit symptoms similar to the ones of natural disease, widening thus the notion of curative similitude: 'every substance capable to provoke certain symptoms in healthy individuals (due to the primary action of the drug), can be used to cure similar symptoms in the sick (through the secondary reaction of the organism), according to the therapeutic similitude principle' (*Organon,* paragraphs 24–28).

Hahnemann claimed that such secondary action is observed "in each and every instance with no exceptions",

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with substantial or infinitesimal doses, in both healthy and ill individuals, raising the principle of similitude to the level of "natural law of cure" (*Organon*, paragraphs 58, 61, 110−112).

Criticizing the method of treatment by contraries (enantiopathic, antipathic or palliative treatment), which "after such short antipathic amelioration, aggravation follows in every case without exception" (*Organon*, paragraphs 58, 59, 65), Hahnemann refers to the serious damage that this secondary action of the organism can bring to the health condition, as "another, more serious disease or, frequently, incurability, even danger of life and death itself" (*Organon*, paragraphs 60, 61).

In the terms of modern pharmacology, Hahnemann's 'primary action' corresponds to the 'therapeutic, adverse and side effects' of conventional drugs, whereas the 'secondary action' (vital or homeostatic reaction) corresponds to the 'rebound effect' or 'paradoxical reaction' of the organism, appearing after the discontinuance or alteration of dosage (*withdrawal syndrome*) of drugs acting contrarily to the symptoms of diseases.

As I have pointed out in previous studies,[3−11] the properties of the rebound effect are the same as the secondary action or vital reaction described by Hahnemann: (i) it appears only in susceptible individuals, who present in their constitution similar symptoms to the pathogenetic effects of the substance; (ii) it does not depend on the substance, repeated doses or type of symptoms (disease); (iii) it appears after the primary action of the substance, as an automatic manifestation of the organism; (iv) it induces an organic state opposite and greater in intensity and/or duration to the primary action of the substance; (v) its magnitude is proportional to the intensity of the primary action of the substance. The rebound effect of modern drugs can also be used in a therapeutic sense, stimulating curative homeostatic reactions.[12,13]

Broadening such evidence to a new drug class, this study describes scientific research demonstrating secondary worsening (paradoxical or rebound) of multiple sclerosis (MS) after discontinuation of natalizumab, a human monoclonal antibody (immunomodulatory drug or biologic response modifier) whose intended primary action is improvement in the disease progression.

Methods

I reviewed the literature (2002−2012) using the Medline database and the keywords 'multiple sclerosis (MS)', 'natalizumab', 'rebound', 'progressive multifocal leukoencephalopathy (PML)' and 'immune reconstitution inflammatory syndrome (IRIS)', selecting the most consistent papers and discussing the scientific evidences according to Hahnemann's postulates.

Results

MS and natalizumab

MS is an inflammatory demyelinating disease of the central nervous system (CNS) that affects some 2.5 million people worldwide. Although the exact disease mechanism is not completely clear, it is known that both environmental and genetic factors influence the development of MS. MS usually starts in the third or fourth decade of life and follows a relapsing clinical course, the most common form is: relapsing-remitting MS (RRMS). The majority of these patients enter a disease phase characterized by continuous, irreversible neurological decline: secondary progressive MS (SPMS). Approximately 50% of all patients require help in walking 15 years after diagnosis, the median time to reaching a high degree of disability is some 30 years. A substantial percentage of MS patients have their first attack during childhood.[14−16]

The objective of any therapy seeking to modify MS is to reduce the frequency and severity of relapse, and to prevent or delay evolution toward a progressive phase. The evidence available suggests that MS is a disease of autoimmune etiology and its treatment is currently based on immunomodulatory drugs such as glucocorticosteroid, interferon (IFN), glatiramer acetate, natalizumab, fingolimod, among others. Current hypotheses hold that a core event in the pathogenesis of MS is the activation of autoreactive T lymphocytes in the periphery that, after proliferating and crossing the blood−brain barrier, trigger a cascade of inflammatory events in the CNS culminating in axonal demyelination and damage. The migration of leukocytes across the blood−brain barrier requires the interaction between adhesion molecules expressed on the cell surface, such as selectins and integrins, and their endothelial receptors. In particular, the combination of the high affinity between $\alpha4\beta1$ and $\alpha4\beta7$ integrins and the vascular cell adhesion molecule-1 (VCAM-1) allows the cells to adhere to the vascular endothelium and initiate transendothelial migration.[17]

Natalizumab (Tysabri) is a humanized monoclonal antibody that keeps leukocytes from migrating across the blood−brain barrier. In May 2012, approximately 99,600 MS patients had received natalizumab worldwide, for at least 12 months.[18] With an IgG4 structure, natalizumab is a selective adhesion molecule inhibitor that recognizes and binds specifically to the $\alpha4$ subunit of $\alpha4\beta1$ and $\alpha4\beta7$ integrins. This drug blocks binding between the endothelial VCAM-1 and the $\alpha4\beta1$ and $\alpha4\beta7$ integrins expressed on the surface of activated T lymphocytes and other mononuclear leukocytes, keeping them from adhering to the endothelium, preventing cell migration and recruitment toward the parenchyma, and the subsequent inflammatory activity in the CNS. Natalizumab has a good risk-benefit ratio in MS patients, reducing the frequency of outbreaks, the progression of disability, and the lesions quantified by neuroimaging. It has also been investigated for the treatment of Crohn's disease and rheumatoid arthritis (RA).[15,19,20]

When doses of between 1 and 3 mg/kg of natalizumab are administered to healthy volunteers or to MS patients, drug concentrations are detectable in blood for 3−8 weeks. After a single dose, peak serum concentrations are reached slowly, over the course of 1−2 h following administration, despite the fact that the drug is distributed mainly in the