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REVIEW

Biological therapies (immunomodulatory drugs), worsening of psoriasis and rebound effect: new evidence of similitude

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Background: **Employing the secondary action or adaptative reaction of the organism as therapeutic response, homeopathy uses the treatment by similitude (*similia similibus curentur*) administering to sick individuals the medicines that caused similar symptoms in healthy individuals. Such homeostatic or paradoxical reaction of the organism is scientifically explained through the rebound effect of drugs, which cause worsening of symptoms after withdrawal of several palliative treatments. Despite promoting an improvement in psoriasis at the beginning of the treatment, modern biological therapies provoke worsening of the psoriasis (rebound psoriasis) after discontinuation of drugs.**
Method: **Exploratory qualitative review of the literature on the occurrence of the rebound effect with the use of immunomodulatory drugs [T-cell modulating agents and tumor necrosis factor (TNF) inhibitors drugs] in the treatment of psoriasis.**
Results: **Several researches indicate the rebound effect as the mechanism of worsening of psoriasis with the use of efalizumab causing the suspension of its marketing authorization in 2009, in view of some severe cases. Other studies also have demonstrated the occurrence of rebound psoriasis with the use of alefacept, etanercept and infliximab.**
Conclusion: **As well as studied in other classes of drugs, the rebound effect of biologic agents supports the principle of similitude (primary action of the drugs followed by secondary action and opposite of the organism).** *Homeopathy* (2016) **105**, 344–355.

Keywords: Homeopathy; Law of similars; Action mode of homeopathic remedies; Rebound effect; Paradoxical reaction; Biological therapy; Monoclonal antibodies; TNF antagonists; Psoriasis

Introduction

In the ancient Greece, Hippocrates recommended treatment of diseases by the principle of contraries (*contraria contrariis curentur*) or by the principle of similars (*similia similibus curentur*) teaching that "*whatever evil and from where come, you might want to always treat or by contrary or by similar*" (*Liber de locis in homine*). Based on *Corpus Hippocraticus*, several exponents of the old medical schools spread these ways to treat.[1]

During the development of the homeopathic method of treatment, Samuel Hahnemann using phenomenological research method to describing the effects of dozens of drugs in the human health and correlating his observations with evidences from medical literature. In the work that inaugurated the homeopathy (*Essay on a new principle for ascertaining the curative power of drugs*)[2] and in the introduction of the *Organon of medicine*[3] he cited several reports of an 'opposite secondary action of the organism' after a 'primary action of the drugs' described in your observations and in hundreds of bibliographical references. These descriptions were illustrated with many 'examples of accidental homeopathic cure' reported by doctors of

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all times, supporting a scientific rationale for the principle of similars.

With these evidences, Hahnemann gathered strong arguments that enabled him to induce, through the Aristotelian inductive logic or *modus ponens*, a physiological mechanism to explain this bidirectional action of drugs on the organism:

"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).

He exemplifies this biphasic action (primary action of the drug followed by a secondary and opposite action of the organism) in the non-pharmacological interventions and in the pharmacological effects of enantiopathic (contrary, antipathic, palliative) treatments used in his time (*Organon*, paragraphs 56−61, 65−67). Based on various examples, he concludes that "*after such short antipathic amelioration, aggravation follows in every case without exception*" (*Organon*, paragraph 58), *i.e.*, after a primary action of palliative medicines occurs a secondary action of the organism, with worsening of initial symptoms.

Proposing to apply such secondary action in a curative way, awakening a adaptative reaction of the organism against its own disorders, Hahnemann suggested employ medicines that provoke signs and symptoms similar to the natural disease, systematizing the application of the curative principle by the similars (homeopathic method of treatment): every substance capable of provoking 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 curative secondary action of the organism), according to the therapeutic similitude principle (*Organon*, paragraphs 24−28).

It is noteworthy that Hahnemann also employed the principle of therapeutic similitude with ponderable (massive) doses of medicines, awakening a curative secondary action of the organism to conduct a complete recovery. For example, in the work that inaugurates the homeopathy,[3] Hahnemann mentions the use of drugs of his time in the homeopathic treatment of numerous diseases and epidemics, applying them according to the principle of similitude ('adverse/side effects' mentioned in literature) and substantial (massive) doses. In *The Lesser Writings*,[4] Hahnemann describes similar applications in other epidemic diseases (remittent and scarlet fevers, typhus, cholera, etc).

Thus, noting the cited manifestation in the most diverse situations, Hahnemann raises the principle of therapeutic similitude (an opposite curative secondary action of the organism after the primary action of the medicine) to the level of 'natural law of cure' or 'law of similars' (*Organon*, paragraphs 26−28, 50−53), **regardless of the doses**, since the symptomatic individualization was respected.

Similitude in modern pharmacology

Providing a connection between the principle of similitude and the modern pharmacology, one can find countless reports in clinical and experimental studies describing the secondary reaction of the organism opposed to the primary action of the drugs, which confirm Hahnemann's theory. Such secondary reaction of the organism is known as 'rebound effect' by modern pharmacology, line of research that we have seen studying systematically in recent decades.[5−21]

According to Webster's New World Medical Dictionary,[22] 'rebound effect' means "*the production of increased negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it was used to treat may come back even stronger when the drug is discontinued or loses effectiveness*". By definition, the manifestation of the rebound effect always reaches an intensity and/or frequency greater than the disturbance initially suppressed by the antipathic drug, causing a worsening of the natural disease and occurs after a given period of time, which depends on the duration of drug effect (biological half-life). Such physiological processes or homeostatic mechanisms are present at all levels of the biological organization from the simplest of cells to the most complex mental and emotional functions, and is not dependent of the disease, type of drug, doses or duration of treatment.[23−25]

Illustrating the universality of the phenomenon, the rebound effect manifests itself after the discontinuation of numerous classes of drugs: vasodilator agents, antihypertensives, antiarrhythmics, antithrombotics, antihyperlipidemics, psychiatrics (anxiolytics, sedative-hypnotics, psychostimulants, antidepressants or antipsychotics), analgesics, anti-inflammatories, diuretics, anti-dyspeptics, bronchodilators, antiresorptives, and immunomodulators, among others.[5−21]

Although such phenomena appearing in a minority of individuals in view of their idiosyncratic nature, contemporary evidences point to the occurrence of severe and fatal iatrogenic events as a function of the rebound effect of many drug classes.[8−19]

Despite the fact that the drug withdrawal is a prerequisite for the manifestation of the phenomenon, studies showed that the rebound effect may also occur even during treatment as a result of the ineffectiveness of the treatment (nonresponders patients) or by phenomenon of tolerance, tachyphylaxis or desensitization (adaptation of the organism to the drug with the loss of pharmacological effect).[5−9,11,13,19,21] On the other hand, the slow and gradual decrease of the doses, avoiding an abrupt discontinuation, is a procedure to minimize the manifestation of the rebound effect.

Broadening the scope of these evidences with a new drug class, this study describes the scientific works demonstrating the worsening of psoriasis ('rebound psoriasis') after the discontinuation of some classes of immunomodulatory drugs employed by recent and innovative

biological therapy. In accordance with the therapeutic similitude principle, we will suggest the use of modern drugs in the treatment of psoriasis, employing the rebound effect in a curative way.

Methods

To increase the body of evidence of the homeopathic principle through the study of the rebound effect of immunomodulatory drugs employed in the treatment of psoriasis, an exploratory qualitative literature review was performed in medical databases (PubMed, Scopus and Web of Science) using the keywords 'psoriasis', 'rebound', 'withdrawal', 'paradoxical', 'biological therapy', 'immunomodulatory drug', 'TNF antagonist', 'TNF blocker', 'monoclonal antibody', 'efalizumab', 'alefacept', 'etanercept', 'adalimumab', 'infliximab'. The articles were selected based on their titles and abstracts, and the full texts of those that addressed the investigated subject were analyzed, as were studies cited by these articles that were not detected by the initial survey. The studies considered most relevant were included in the present review of the clinical and experimental evidences of the rebound effect in the biological treatment of psoriasis.

Results

Psoriasis and biological therapies (immunomodulatory drugs)

Psoriasis is a skin inflammatory autoimmune disease, which affects up to 2% of the population worldwide. It has been shown that the severity of the disease is influenced by genetic and environmental factors. The physical and emotional impact on the quality of life of affected individuals is similar to that associated with other chronic diseases. In the spectrum of the disease, the most common type is chronic plaque psoriasis that shows well demarked plaques covered by silver scales which are often located symmetrically and bilaterally. The extensor surfaces (elbows and knees), the lower back, scalp, and the nails are involved more often. In severe cases the plaques can affect the whole body. Approximately 30% of the patients suffer from psoriatic arthritis, which is a sero-negative inflammatory arthritis with variable course.

Between 20 and 30% of patients require systemic treatment. Mild forms of psoriasis can be controlled by topical treatment (such as topical steroids, vitamin D derivates, selective retinoids, anthralins etc.), whereas the therapy of moderate to severe forms consists of phototherapy (ultraviolet B light or psoralen plus ultraviolet A light) combined with a variety of systemic treatment forms, such as methotrexate, ciclosporin, oral retinoids, 6-azathioprine, and fumaric acid. However, all of these therapeutic options are limited: topical treatment is unsuitable to treat larger areas; chronic steroid use has common adverse events, such as skin atrophy, striae, and telangiectasia. Phototherapy can lead to photo-aging of the skin and to an increased risk of skin cancer. Besides that, long-term use of the systemic agents (methotrexate, ciclosporin etc.) is limited by serious side-effects including myelosuppression, hepatotoxicity, impairment of the renal function and teratogenicity, among others.[26]

Psoriasis is regarded as a Th1 pre-dominated inflammatory autoimmune disease. It is supposed that after contact with an unknown antigen, a subset of T cells develops into memory $CD4^+$ and $CD8^+$ T cells. These cells proliferate and migrate from the lymphnodes to the skin where they initiate a cutaneous inflammatory reaction and the production of pro-inflammatory mediators (the number of T cells infiltrating the skin may be correlated with disease activity of psoriasis). In the last decade, advancements in understanding the pathogenesis of psoriasis, including the role of T cells and cytokines, have been crucial to the development of biological therapies.

The term 'biological' refers to agents synthesized from the products of living organism whom modulate the immune system through stimulatory or inhibitory actions, acting at only specific parts. In psoriasis, the biological agents act by selectively inhibiting the activation and maturation of antigen-presenting cells, by blocking the secretion of cytokines, and by inhibiting the activation and proliferation of T lymphocytes, their migration to the skin, their effector function, or their reactivation. Despite their safety profile be considered more favorable than conventional systemic agents (without causing generalized immunosuppression), the initial enthusiasm has been replaced by a cautious approach with increasing years of experience with these new drugs. Generally, biological therapies for psoriasis can be classified into two main categories: the T-cell modulating agents (efalizumab and alefacept) and the tumor necrosis factor-alpha (TNFα) inhibitors drugs (etanercept, infliximab and adalimumab).[27,28]

T-cell modulating agents (efalizumab and alefacept)

Efalizumab (Raptiva®) is a human monoclonal IgG1 antibody that binds to the alpha-subunit of lymphocyte function associated antigen (LFA)-1, blocking the interaction between LFA-1 and intercellular adhesion molecule-1. The result is a reduction in T cell activation, an inhibition of the trafficking and recruitment of T cells to the dermis and epidermis, and a decrease in the reactivation of T cells at several steps in the psoriasis pathogenesis. The half-life is approximately 6 days.[29,30]

Alefacept (Amevive®) is a recombinant dimeric human fusion protein which consists of the CD2-binding portion of the leukocyte function antigen-3 (LFA-3) linked to the Fc portion of the IgG. Alefacept binds competitively to the CD2 on the surface of T cells with the LFA-3 portion of the drug and efficiently interferes with LFA-3/CD2 binding and thereby T cell activation, whereas the Fc portion of alefacept engages the immunoglobulin receptor FcγRIII on the surface of natural killer cells (and macrophages) resulting in apoptosis of specific memory T cell subsets. These effects produce a selective reduction in memory-effector (CD4+CD45RO+ and CD8+CD45RO+) T cells, the source of the clonal precursors that emigrate from the blood, and drive the disease in the skin, while having

relatively no effect on naive T-cell populations. The half-life is approximately 12 days.[31]

TNF inhibitors drugs (etanercept, adalimumab and infliximab)

TNFα is a pleiotropic cytokine with both proinflammatory and immunoregulatory functions that induces macrophages and other cells to secrete pro-inflammatory cytokines such as interleukin (IL-1, IL-6, IL-8 and others), leads to T-cell activation, and causes endothelial cells to express adhesion molecules. TNFα is synthesized as pro-TNF (26 kDa), which is bound to the membrane and released upon the cleavage of its pro-domain by the TNF-converting enzyme (TACE). TNFα acts *via* two distinct receptors (TNFR-1 and TNFR-2), although its affinity for TNFR-2 is five times higher than its affinity for TNFR-1. TNF mediates a variety of direct pathogenic effects and induces the production of other mediators of inflammation and tissue destruction, placing it at the head of an inflammatory cascade within an inflammatory network. At low concentrations in tissues, TNF is thought to have beneficial effects, such as the augmentation of host defense mechanisms against infections. At high concentrations, TNF can lead to excess inflammation and organs injury, relating to pathogenesis of various chronic inflammatory diseases.[32,33]

TNFα is mainly produced by activated macrophages, T lymphocytes, and natural killer cells, but is also expressed at lower levels by fibroblasts, smooth muscle cells, and tumor cells. Its complex functions in the immune system include the stimulation of inflammation, cytotoxicity, the regulation of cell adhesion, and the induction of cachexia. As it plays a key role in the pathogenesis of chronic immune-mediated inflammatory diseases such as rheumatoid arthritis (and others autoimmune arthritis), ankylosing spondylitis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), psoriasis (psoriatic arthritis), among others, the TNF antagonists (anti-TNF, TNF blockers or TNF inhibitors) drugs has been developed in an attempt to neutralize its biological activities. The most widely used anti-TNF for treating psoriasis are the recombinant TNF receptor (etanercept) and the two monoclonal antibodies (infliximab and adalimumab).[33,34]

Although these drugs have similar mechanisms of action, they have different structures, morphology, pharmacokinetic properties, action and immunogenicity, and there are differences in patient responses that may be due to differences in bioavailability, the stability of the drug/TNF complex, the development of anti-drug antibodies and, possibly, treatment compliance (Table 1).

Psoriasis, biological therapies and rebound effect

In the treatment of psoriasis with immunomodulators, the rebound phenomenon is an adverse event commonly described. While 'relapse' of the disease can be applied only to 'responders' to treatment, those who attained a 50% or better improvement in Psoriasis Area and Severity Index (PASI) score from baseline (*i.e.*, PASI 50), 'rebound' occur with 'responders' and 'nonresponders', and is defined as a PASI score 125% or greater of baseline or change in morphology (generalized pustular, erythrodermic or increased inflammatory psoriasis) within 3 months of stopping treatment. Generally, the rebound phenomenon manifests itself after the suspension of the treatment, in a superior period to the biological half-life of the drug.[35–38] However, as mentioned initially, it is worth emphasizing that 'the rebound effect can also be awakened during the treatment', as a result of the ineffectiveness of the treatment or the phenomenon of tolerance, tachyphylaxis or desensitization (adaptation of the organism to the drug with the loss of pharmacological effect).

Clarifying this placement, remember that the manifestation of the rebound effect (secondary action) is not dependent of the disease, type of drug, doses or duration of treatment, arising as an automatic mechanism of self-regulation after cessation of the primary action of the drug, in order to maintain the balance of the internal environment (homeostasis). In view of this, as occurs with infinitesimal doses of homeopathic medicines, the rebound phenomenon can be aroused during a treatment with 'minimum action' of conventional medicines, condition observed in patients in whom the drug is ineffective ('nonresponders' to treatment). The phenomenon of tolerance during the treatment can also make the drug ineffective ('nonresponders'), allowing the same manifestation of the rebound effect.

The biological agents vary considerably in terms of their long-term of effect: alefacept had the longest off-treatment benefit (29.9 weeks in PASI 75 responders), followed by infliximab (19.5 weeks), adalimumab (18 weeks), etanercept (12.1 weeks in PASI 50 responders), and, lastly, efalizumab (9.6 weeks). In addition to the rebound effect studied in this review, immunomodulatory drugs cause other adverse events such as influenza-like syndromes, headache, laboratory abnormalities (presence of antinuclear antibodies, increased white cell count, liver enzymes and cholesterol/

Table 1 Currently available anti-TNF drugs and their disease indications

Drug (brand) name/Structure	*Half-life*	*Disease indications*
Etanercept (Enbrel®)/Human recombinant fusion protein: TNFR2 IgG1-Fc	2–4 weeks	Rheumatoid arthritis; Polyarticular juvenile idiopathic arthritis; Psoriatic arthritis; Ankylosing spondylitis; Plaque psoriasis
Infliximab (Remicade®)/Humanized (chimeric) IgG1k mAb	4 weeks	Rheumatoid arthritis; Psoriatic arthritis; Ankylosing spondylitis; Plaque psoriasis; Crohn's disease
Adalimumab (Humira®)/Human IgG1k mAb	2–4 weeks	Rheumatoid arthritis; Psoriatic arthritis; Plaque psoriasis; Ankylosing spondylitis; Crohn's disease; Juvenile idiopathic arthritis

triglycerides etc.), infections (upper respiratory tract, acute gastroenteritis, urinary tract, tuberculosis etc.), tumors, congestive heart failure (CHF), demyelinating disease, autoimmune diseases, and others.

T-cell modulating agents and rebound psoriasis

Efalizumab withdrawal and rebound effect: Efalizumab, a recombinant humanized immunoglobulin G-1 monoclonal antibody, is administered by weekly subcutaneous injection. The initial dose in the first week is 0.7 mg/kg and this is increased to 1 mg/kg in the following weeks. Treatment duration is 12 weeks and can be continued in patients with a good response to the drug.

The most notorious cutaneous effect connected to efalizumab is the rebound effect (exacerbation of psoriasis or change in morphology), and several studies have demonstrated this phenomenon after discontinuation of the drug. In the initial phase III randomized placebo-controlled trial (RCT)[39] conducted by Genentech Inc. (Roche) for licensing, rebound was identified in 12.6% (152/1201) of patients, with patients experiencing PASI 125 or change in morphology to guttate, erythrodermic, or pustular psoriasis. Others phase III RCTs showed similar results.[40–44]

In a retrospective analysis of pooled data from different studies, Gordon *et al.*[35] showed that 14% of patients presented rebound (worsening of psoriasis to ≥125% of the initial PASI) after abrupt withdrawal of efalizumab treatment. Carey *et al.*[45] presented a summary of pooled data from various phase III RCTs in which patients received treatment for 12−24 weeks, with an off-treatment observation period following: rebound also was experienced in 14.3% (188/1316) of patients.

While Selenko-Gebauer *et al.*[46] reported the occurrence of 14% of rebound psoriasis after discontinuation of efalizumab in 220 patients accompanied at the Department of Dermatology of the Medical University of Vienna, Sánchez-Regaña *et al.*,[37] in a survey of the Spanish Psoriasis Group, described rebound psoriasis after discontinuation of efalizumab in 20.9% (64/306) of patients.

Menter *et al.*[47] conducted a multicenter open-label study with 130 patients regarding the main aspects of the rebound phenomenon during the transitioning of the efalizumab to other drugs. In this transition phase ('drug withdrawal'), rebound was observed in 16 of 128 (12.5%) patients for whom follow-up was available: no incident of rebound was observed in the responder group (46 patients; PASI 75); two of 32 (6.3%) intermediate responders and 14 of 49 (28.6%) nonresponders experienced rebound. Serious rebound events were observed in nine nonresponders patients (9/16 or 56%) and all received transition therapy: severe erythrodermic exacerbations of psoriasis (4/16 or 25% of patients), severe atypical papular changes (4/16 or 25%), pustular psoriasis exacerbation (1/16 or 6%) and serious and severe erythrodermic psoriasis (1/16 or 6%). The results showed that the number of patients who experienced rebound at any given weekly period was low (maximum 6.4%), most rebound events occurred within 4−9 weeks following efalizumab discontinuation, and rebound events that occurred generally did not last longer than about 5 weeks. In the 12 weeks after the last efalizumab dose, arthritis adverse events were observed in 2.5% (4/16) of patients (one responder and three nonresponders) with pre-existing psoriatic arthritis: although the authors do not identify as such, these manifestations, probably, are result of the rebound effect, as we will see below. The authors concluded that efalizumab nonresponders are at higher risk of developing rebound.

Tsai *et al.*[48] conducted an open-label study of patients receiving efalizumab for 12 weeks, followed by an observation period: rebound phenomenon was seen in 17.7% (8/45) of patients. A cohort study[49] was carried out with patients receiving efalizumab for at least 3 months, showing the occurrence of rebound psoriasis in 22.6% (7/31) of patients: this occurred while on treatment in 45.5% (5/11) of nonresponders patients (tolerance phenomenon, probably) and after discontinuation of treatment in 10% (2/20) of patients with good response (responders), contrasting the observed by Menter *et al.*[47] Rebound led to erythrodermic psoriasis in 6.45% (2/31) and psoriatic arthritis in 3.2% (1/31) of patients. With similar results, other multicenter open-label study[50] showed that 11% (14/127) of responders experienced rebound after the suspension of efalizumab treatment, and 9.2% (37/402) of nonresponders experienced rebound during the first-treatment period; 12.9% (52/402) of nonresponders experienced disease exacerbation at some point during the trial.

Despite initially favorable, the safety profile of efalizumab revealed the appearance of severe adverse events (progressive multifocal leukoencephalopathy or PML) in long-term treated patients inducing the European Medicines Agency recommended the suspension of the marketing authorization for efalizumab in February 2009.[30] PML is a rare, potentially fatal demyelinating disease characterized by multiple foci of demyelization affecting mainly the subcortical white matter in the brain and may manifest as a variety of neurological symptoms, including visual deficits, motor weakness, and behavior or cognitive changes.[51] As we will discuss below, the occurrence of PML with efalizumab can be explained by the immune reconstitution inflammatory syndrome (IRIS-PML), a secondary (rebound) effect of the organism in response to the primary immunosuppressive action of the drug.

Evaluating the course of psoriasis following this forced drug withdrawal, Morell *et al.*[52] conducted a multicenter observational study with 147 patients treated in twelve Spanish hospitals: rebound following withdrawal of efalizumab was observed in 30% (44/142) of patients, and the likelihood of phenomenon was independent of clinical characteristics, duration of treatment or response (responders to treatment or nonresponders), or therapeutic approach used by the dermatologist following suspension (reiterating 'the common properties of the rebound effect' initially cited). The authors concluded that "*there was a high frequency of rebound following suspension of efalizumab, exceeding the rate reported in pivotal trials.*[39–45] *This is a particularly noteworthy given the large*

proportion of patients with a good response to treatment and therefore believed to have a better prognosis". The average time of manifestation of the phenomenon was 6 weeks after discontinuation of efalizumab, and the rebound manifests itself usually in the form of a morphological change with respect to the prior psoriasis: generalized appearance of guttate psoriasis or small plaques (66% or 29/44 patients), pustular psoriasis (16% or 7/44), inflammatory forms (14% or 6/44), erythrodermic forms (2% or 1/44) and arthropathic forms (2% or 1/44). Twenty-seven patients (61%) required another drugs (ciclosporin, methotrexate, etanercept, adalimumab or infliximab) to manage rebound, although often are not able to stop the rebound phenomenon triggered.[47,53–55]

Illustrating this aspect (no resolution of the rebound effect despite the administration of other immunosuppressive drugs), Baniandrés *et al.*[56] performed a prospective follow-up study with 32 patients after efalizumab discontinuation and transition therapy. Even though 92.8% of the patients were considered good responders (>75% reduction in PASI score), 25% of the group (8/32) experienced rebound; the mean length of time between efalizumab discontinuation and the appearance of the rebound flare was 47 days. The percentage of patients in whom rebound was observed on transition therapy was 18% (2/11) for ciclosporin, 50% (1/2) for methotrexate, 50% (1/2) for adalimumab, 50% (1/2) for etanercept, and 27% (3/11) for topical treatment. The authors observed a very high rate of rebound psoriasis and generalized inflammation in patients whose disease had previously been well controlled for several years.

An estimate of the frequency of rebound psoriasis with efalizumab is described in Table 2, which varies around 10–30% according to several studies. Worth to mention also that the most rebound events occurred within 4–9 weeks following efalizumab discontinuation (the half-life of the drug is 6 days, and their long-term of effect is 9.6 weeks), and rebound events that occurred generally did not last longer than about 5 weeks.[47,52,56]

Alefacept withdrawal and rebound effect: Alefacept, a human recombinant dimeric fusion protein, inhibits activation of memory-effector T lymphocytes and reduces the number of CD4+, CD8+, and CD45RO+ cells, responsible for the formation of psoriatic plaques. It is typically administered in a dosing regimen of 15 mg intramuscularly (IM) weekly for 12 weeks.

In a small cohort study, Cafardi *et al.*[57] reported two cases (2/8 or 25% of patients) with rebound morphological change from plaque psoriasis to erythrodermic forms: one patient with erythroderma was hospitalized during the dosing regimen of 15 mg (IM) of alefacept.[58]

TNF inhibitors drugs and rebound psoriasis (Table 3)

Etanercept withdrawal and rebound effect: Etanercept is a human recombinant fusion protein containing TNF receptor immunoglobulin fusion protein, acting as a competitive antagonist of endogenous TNF by blocking the interaction with cell-surface receptors, thereby inhibiting its proinflammatory activity. The recommended dose is 25 or 50 mg subcutaneous twice weekly for 12–24 weeks.

In a survey of the Spanish Psoriasis Group, Sánchez-Regaña *et al.*[37] described rebound psoriasis (palmoplantar pustular psoriasis) in 0.9% (4/439) of patients who received etanercept. In a retrospective, observational study of patients with moderate to severe psoriasis plaque, who received continuous treatment with etanercept for more than 24 weeks, the rebound effect was observed in 4.6% (2/43) of patients, as a result of temporary interruption of treatment or dose reduction (50 mg–25 mg).[59]

In another retrospective study,[54] 35 patients with high-need psoriasis plaque who were unable to continue efalizumab were immediately switched to etanercept, in

Table 2 T-cell modulating agent (efalizumab) and rebound psoriasis

Authors	*Type of study*	*Number of patients*	*Frequence of rebound psoriasis*
Genentech Inc.[39]	RCT	1201	12.6% (152/1201)
Carey *et al.*[45]	RCTs (pooled data)	1316	14.3% (188/1316)
Selenko-Gebauer *et al.*[46]	Retrospective cohort	220	14% (31/220)
Sánchez-Regaña *et al.*[37]	Retrospective cohort	306	20.9% (64/306)
Menter *et al.*[47]	Multicenter open-label	128	12.5% (16/128)
Tsai *et al.*[48]	Open-label	45	17.7% (8/45)
Puig *et al.*[49]	Prospective cohort	31	22.6% (7/31)
Lotti *et al.*[50]	Multicenter open-label	529	9.6% (51/529)
Morell *et al.*[52]	Multicenter open-label	142	30.9% (44/142)

Table 3 TNF inhibitors drugs (etanercept; infliximab) and rebound psoriasis

Authors	*Type of study/drug*	*Number of patients*	*Frequence of rebound psoriasis*
Sánchez-Regaña *et al.*[37]	Retrospective cohort/etanercept	439	0.9% (4/439)
Zaragoza *et al.*[59]	Retrospective cohort/etanercept	43	4.6% (2/43)
Antoniou *et al.*[54]	Retrospective cohort/etanercept	12	16.6% (2/12)
Antoniou *et al.*[54]	Retrospective cohort/etanercept and methotrexate	11	18.1% (2/11)
Puig *et al.*[60]	Case series/infliximab	43	4.6% (2/43)

combination with other drugs or in monotherapy: in group that received methotrexate/etanercept combination therapy (n = 11) there was 2 rebound psoriasis (18%), and in group that received etanercept monotherapy (n = 12) there was 2 rebound psoriasis (16.6%); there was no rebound in group that received ciclosporin/etanercept combination therapy (n = 12).

Infliximab withdrawal and rebound effect: Infliximab is a chimeric monoclonal antibody against TNF-α that binds both soluble and transmembrane TNF-α and neutralizes its proinflammatory activity. The recommended dose is 5 mg/kg body weight in weeks 0, 2, and 6, and then every 8 weeks after.

In the largest case series (contributed by L. Puig),[60] which comprised 43 patients, 20.9% (9/43) of patients had infusion reactions: in 4.6% (2/43) of these patients, the development of a severe acute infusion reaction was preceded by a loss of response or rebound effect (PASI >125% of baseline). In 2.3% (1/43) of these patients, the severe infusion reaction was associated with self limiting arthritis in the ankle: the onset of the arthritis was associated with a rebound in the severity of psoriasis (PASI >125% of baseline) and occurred before the infusion reaction. Another independent study showed similar results.[61]

Although the authors, generally, do not characterize the worsening of psoriasis 'during' treatment with TNF antagonists' as rebound psoriasis (by classical definition, the rebound effect occurs 'after discontinuation' of the drug), several studies[62–72] described "*exacerbation of previous psoriasis with change in morphology (guttate, erythrodermic, or pustular forms)*" developed during the course of treatment with TNF antagonists (etanercept, adalimumab and infliximab) in some patients, which may be considered likely rebound psoriasis in the presence of the 'tolerance phenomenon', as described initially.

These biases of interpretation is notorious in a recent review[70] regarding the paradoxical psoriasiform reactions during TNFα therapy, in which the authors rule out the occurrence of apparent rebound phenomena based on the fact that "*exacerbations of previous psoriasis with changes in morphology occurs without discontinuation of the drug*": "*Nor should they be confused with a flare-up of psoriasis, which is typically defined as a deterioration of the psoriasis of more than 125% compared to the baseline situation, or a change in morphology induced by the biological agent, but after its interruption. The changes in morphology to which we are referring in this section occur without discontinuation of the drug*". Reiterating this partial or biased assessment of the phenomenon, the authors recommend for the management of severe cases of exacerbation or change in morphology of psoriasis the same general measures described in the management of the rebound effect: "*combined therapy with another systemic treatment (preferably, with a rapid response and different mechanism of action) such as ciclosporin or methotrexate*".

Discussion

IRIS-PML: exuberant immune-inflammatory response (rebound) after immune-inflammatory suppression

Expanding the source of evidence that provides the scientific basis to the similitude principle, we published, in 2013, a review that demonstrated the secondary worsening of multiple sclerosis (MS) after suspension of natalizumab, a human monoclonal antibody that suppresses the disease inflammatory activity as primary action.[17] Regardless the cited relationship between the human polyomavirus JC (JCV) and the progressive multifocal leukoencephalopathy ('PML' or 'JCV-PML'), several studies relate the IRIS as the more feasible explanation of the described 'PML' ('IRIS-PML' or 'CNS IRIS sans PML'), a significant MS reactivation (exacerbation of symptoms or enlarging lesions or increased gadolinium on cerebral magnetic resonance imaging) after natalizumab withdrawal: a rebound effect or secondary action of the organism in response to the primary immunosuppressive action provoked by the drug.[17] This phenomenon continues to be described also with other classes of immunomodulatory drugs (fingolimod, for example) employed in the treatment of MS.[73–80]

In view of efalizumab be a human monoclonal antibody with structure and action similar to natalizumab, it also presents similar explanation for the rebound effect: after a primary reduction in T cell activation by the direct action of the drug, occurs a secondary reactivation of T lymphocytes in lymphnodes, increasing the circulating lymphocytes and exacerbating the trafficking and recruitment of T cells to the dermis and epidermis, which promote hyperproliferation and abnormal differentiation of keratinocyte (rebound psoriasis).[81] Analogously, the occurrence of cases of 'PML' with efalizumab[29,30] can be explained by the IRIS-PML, in which "*the rebound restoration of immune and inflammatory response is overwhelming with potentially fatal results*", as we described with natalizumab.[17,82]

"[…] the Immune Reconstitution Inflammatory Syndrome (IRIS) can be identified as a consequence of therapy discontinuation leading to a dysregulated inflammatory response to infectious and noninfectious antigens during immune recovery, after an induced immune down regulation determined by previously administered agents. […] The pathogenesis of IRIS is ultimately based on a rapid and often exuberant immune-inflammatory response of the host to resident microbial antigens or on a specific homeostatic rebound. […] In the case of local IRIS-PML, the rebounded situation shows different features. The brain histology showed an extensive infiltration of T cells, particularly CD8+ lymphocytes, B lymphocytes and plasma cells, together with a low number of JCV-infected cells, as compared to classical PML usually encountered in adult and pediatric HIV-infected patients. In fact, the number of T cells in IRIS-PML was found to be up to 9 times higher than in PML, while B-cells and plasma cells were practically absent in the latter, showing instead a higher number

of JCV-infected cells. Taken together, an unbalanced recovery after therapy discontinuation, mainly because of the impairment of the T regulatory cells compartment and the overstimulation of pro-inflammatory cytokines, justifies most of the clinical immune rebound signs, both in infectious and non-infectious situations. […] A number of TB and fungal IRIS have been also observed after TNFα antagonists (infliximab, adalimumab) discontinuation. Notably, a concomitant recovery of reactivity to tuberculin was observed together with the reappearance of granulomatous pulmonary lesions. In some life-threatening cases monoclonal antibodies therapy was reintroduced with beneficial effect on TB-IRIS, thus confirming the link between immunosuppression and IRIS rebounding insurgence. Overall, the immune over-response often appears to be of the granulomatous type, although the predominant cell component is represented by dysregulated expanding CD4+ lymphocytes, which is indicated as the major supporter of IRIS, possibly associated with a hyper-responsiveness of the innate immunity to T cell help. Interestingly, the rebounded inflammatory response tends to be preferably localized, even in those infections (mycobacterial) that are typically disseminated after immunosuppressive therapy, and exuberant even before normal T cell levels appear into circulation, suggesting a protective confining role of IRIS-mediated granulomatous intervention".[83]

Therapeutic use of the rebound effect of modern drugs: new homeopathic medicines

Similarly to the homeopathic method of treatment employed for more than 200 years,[21,84] a new therapeutic approach is currently evolving within modern pharmacology based on the use of substances that induce definite organic dysfunctions to treat similar disorders. Known as 'paradoxical pharmacology',[85–90] it assumes that, "*exacerbating a disease [can] make use of the body's compensatory and redundant mechanisms to achieve a beneficial long-term response*",[85] thus suggesting the use of the paradoxical (rebound) drug effects with therapeutic intention.

That therapeutic method is exemplified by the use of beta-blockers and calcium channel blockers in the treatment of CHF, with consequent improvement of the ventricular contractility and reduction of the associated mortality.[85,89,91,92] Beta-blockers might also be used for chronic treatment of asthma, in which condition they promote bronchodilation and reduce the airway inflammation.[85,89,93] Application of the paradoxical antidiuretic effect of thiazides to the treatment of diabetes insipidus allows reducing polyuria and increasing the urine osmolality.[94] Similarly, arsenic trioxide (As_2O_3), a significant carcinogenic agent, showed much promise as anticancer drug (for instance, in acute promyelocytic leukemia)[95,96]; among many others examples.[90] Analogously to homeopathic treatment,[21,97,98] such bidirectional reaction occurs independent of the dose employed,[90] and the authors suggest "*to start at a very low dose and increase the dose over a period of weeks*".[85]

Aiming at bridging the gap between different therapeutic systems, as well as to broaden the scope of action of the treatment by similar, we elaborated a systematic method of application of the curative rebound effect of drugs. According to this proposal we suggest giving to patients the drugs that cause adverse events similar to the full picture of their characteristic symptoms and signs, but in highly diluted doses (homeopathic potencies) so as to stimulate a homeostatic (rebound or paradoxical) reaction of the organism against its own disorders.[21,99–103]

To operationalize this proposal, we elaborate a Homeopathic Materia Medica of Modern Drugs and a Homeopathic Repertory of Modern Drugs, which includes all the adverse events (primary or pathogenetic effects) of 1250 modern drugs as described in the United States Pharmacopeia Dispensing Information (USP-DI).[104] This program, named "*New Homeopathic Medicines: use of modern drugs according to the principle of similitude*", including theoretical and practical materials, is available at an open-access bilingual (English, Portuguese) website (http://www.newhomeopathicmedicines.com).[105]

Starting the clinical research with this proposal, we are developing a randomized, double-blind, placebo-controlled trial to assess the effectiveness of the potentized estrogen in individualized homeopathic treatment of chronic pelvic pain associated with endometriosis. A total of 50 women with endometriosis, chronic pelvic pain and a set of signs and symptoms similar to the adverse events caused by estrogen were randomly allocated to receive potentized estrogen or placebo. The primary clinical outcome measure will be severity of chronic pelvic pain after 24 weeks of intervention.[106,107]

As we will suggest below, similar protocol can be developed with drugs that cause psoriasis as adverse event (primary action or pathogenetic effect) with the aim of arousing a curative rebound reaction.

Conclusion and suggestion

A large number of severe and potentially fatal adverse events might be avoided if health professionals were oriented to recognize the occurrence of rebound effect following the discontinuation of palliative drugs, thus minimizing the occurrence of disease aggravation by reducing doses gradually and slowly or by restarting the drug.[19] Although these are not traditionally considered adverse events, "*drug discontinuation effects are part of the pharmacology of a drug*",[25] and thus should be included when teaching modern pharmacology.

Despite the different terminologies consequent to scientific knowledge of different times, descriptions and properties of 'secondary action' or 'vital reaction' of the Hahnemann's pharmacological model present similar aspects to the 'rebound effect' or 'paradoxical reaction' of modern pharmacology, indicating the same mechanism of action. Demonstrating its universal character, the rebound effect can occur with all classes of drugs with contrary (enantiopathic or palliative) action to the symptoms of diseases and in different individuals, although it

manifests itself in a minority of individuals in view of its idiosyncratic character.

In the case of efalizumab, the studies estimated the occurrence of rebound psoriasis in 10−30% of patients. The most rebound events occurred within 4−9 weeks following efalizumab discontinuation, and did not last longer than about 5 weeks. Studies with etanercept estimated the occurrence of rebound psoriasis in 1−18% of patients.

Analogously to other immunomodulatory drugs and diseases, efalizumab withdrawal may cause exuberant immune-inflammatory rebound (IRIS-PML) with severe and fatal episodes, evidencing the magnitude that the phenomenon can achieve.

Suggesting the therapeutic use of the rebound effect of modern drugs in the treatment of psoriasis, is described in the Homeopathic Repertory of Modern Drugs,[105] chapter 'Skin', rubric 'Eruptions or Lesions', sub-rubric 'psoriasis, psoriasiform eruption', some conventional drugs (or drug class) that caused psoriasis as adverse event (primary action or pathogenetic effect), which could be used in accordance with the principle of therapeutic similitude to treat psoriatic patients, stimulating a curative reaction of the organism: acitretin, beta-adrenergic blocking agents (ophthalmic, systemic and associated with diuretics), flavocoxid, peginterferon alfa-2b, and ursodiol.

According to recent review,[108] another conventional drugs provoke psoriasis as adverse event, which can also be employed in accordance with the principle of therapeutic similitude: amiodarone, angiotensin-converting enzyme inhibitors, antibiotics (tetracyclines, macrolides and penicillin derivatives), antimalarial agents, benzodiazepines, cimetidine, clonidine, digoxin, fluoxetine, gemfibrozil, gold, imiquimod, interferons, lithium, nonsteroidal anti-inflammatory drugs (topical and systemic), phenylbutazone, quinidine, and terbinafine. Among all drugs that caused psoriasis, the beta-adrenergic blocking agents present the most frequent and intense pathogenetic effect. In this proposal, is worth emphasizing that the individualization of homeopathic medicine in accordance with the symptomatic totality is a fundamental premise for the therapeutic success, and the Homeopathic Materia Medica of Modern Drugs[105] must be used to achieve this goal.

Recently, Bond and Giles[89] encourage the scientists and researchers to examine the paradoxical (rebound) phenomenon systematically, changing the dogma of current treatment and incorporating new approaches to the modern therapeutic arsenal:

"The identification of the phenomena of temporal differences in the effects of both agonists and antagonists in numerous drug classes has, at first observation, seemed extremely paradoxical. However, as scientists, our natural inclination is to ask the question 'why?'. Over the coming years the mechanistic basis for such behavior will undoubtedly be revealed, and the paradox will be no more. […] Nevertheless for those of us who have felt compelled to challenge dogma of current treatment paradigms because we observed paradoxical behavior, the path has been long and challenging. Seemingly 'simple' explanations of mechanism of action of a particular drug class become turned on their head, and obtaining funding, and acceptance of paradigm-shifting ideas by peers, takes many years".

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