

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) ■, 1–12.

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

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