

Low dose cytokine and the psycho-neuro-endocrine-immune approach in dermatology: Here is the future

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Introduction to low dose medicine

In recent years the research in the fields of molecular biology and physiopathology highlighted the pivotal role of signaling molecules (hormones, neuropeptides, cytokines and growth factors) in both physiological and pathological processes in clear accordance with a new unified vision of the biological functions of the body, guiding principle of Psycho-Neuro-Endocrine-Immunology (PNEI) [1-6].

The PNEI vision is centered on the role of the bi-directional cross-talk between the psychoneuroendocrine systems and the immune system managed by a complex network of signaling molecules which are the carriers of the biological information necessary for the homeostatic regulation of all cellular responses. An altered cross-talk due to an imbalance between specific signal molecules is proved to be fundamental for the onset of inflammatory, allergic and autoimmune diseases [7-9].

To preserve and/or recover the homeostatic equilibrium of PNEI axis are the expected goals of Low Dose Medicine (LDM) which suggest the use of biological molecules in order to restore the starting physiological conditions (homeostasis).

LDM represents an innovative medical approach which integrates the most recent knowledge in the fields of Molecular Biology, PNEI and ultra-low doses research.

LDM therapeutic approach is based on messenger molecules *oral administration* in order to:

- *enhance* a pathologically down-regulated cellular pathway administering cytokine, hormone, neuropeptides or growth factor physiologically linked with the altered signalling.
- *re-equilibrate* a biological effect according to the principle of "opposing" molecules.

Scientific literature reports that cytokines oral intake is effective in modulating immune response [10-12] but presents the critical point of a low bioavailability [13]: this pitfall is avoided using an adequate drug delivery system. The use of low doses of active molecules *per os* in LDM (in a range between 10⁻⁹ (nanograms) and 10⁻¹⁵ (femtograms)) is made possible by the application of SKA (Sequential Kinetic Activation) technology, an innovative drug delivery system which allows these ultra-low concentrations to be effective both in basic experimental assays and in clinical therapy even below the actually considered minimum effective dose.

Scientific research has validated the principles of LDM: Since 2009

a growing body of scientific publications [14-18] extended the available data regarding LDM efficacy and safety. Collected data showed the efficacy of low dose SKA cytokines treatment on Th1/Th2/Th17 switch modulation.

LDM in dermatology: An innovative therapeutic approach

The skin defense system is composed of three main levels: the skin barrier, the innate immunity, and the acquired immunity [19,20]. Each layer has a specific role in order to protect the body against external and internal inflammatory triggers and infectious agents. A disorder in a specific layer can reverberate on the others layer and the loss of immune skin homeostasis contributes to the pathogenesis of inflammatory skin diseases.

Numerous dermatologic diseases with an important inflammatory component are characterized by the presence of a shift in the immunological balance which is mainly reflected in an imbalance between the cytokines expressed by Th1 and Th2 lymphocyte subpopulations. The Th1/Th2 paradigm is based on the evidence that Th1 cytokines hyper-production is strictly linked with organ-specific autoimmune diseases; skin diseases such as Psoriasis, Vitiligo and Alopecia Areata fully fall back in this pathological immune plan.

Since the 70s [21] anti-cytokine therapy was studied for the treatment of autoimmune diseases mainly targeting the typical Th1 cytokines IFNs, IL-1 and TNF- α and the use of opposing interleukin and antibodies was tested for Alopecia Areata, Psoriasis and Atopic Dermatis [22-24].

The use of cytokines and other signal molecules often collides with the need of systemic administration (generally *iv* and subcutaneous injections) of high dosages of drugs which show a wide range of dose-dependent side effects in addition to the pharmacological ones [25-27].

Thanks to the LDM approach and the availability of low dose SKA cytokines, growth factor hormones and neuropeptides it is now possible to use lower doses of signal molecules (in the range of pictograms and

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Received: January 02, 2015; **Accepted:** January 12, 2015; **Published:** January 14, 2015

femtograms) with therapeutic results comparable to those induced by high concentrations but without connected side effects.

A multicenter double-blind placebo-controlled clinical study performed by Roberti ML, et al. highlighted the possibility of using specific low dose SKA cytokines (IL-4; IL-10; IL-11, at a concentration of 10 fg/ml GUNA S.p.a. Milan, Italy) for the therapy of Psoriasis Vulgaris.

The efficacy of treatment with low-dose cytokines was evaluated both in terms of improvement of the condition of psoriatic lesions and in the quality of life evaluated using the rating scales PASI (Psoriasis Area Severity Index) and DLQI (Dermatology Life Quality Index) for the evaluation of the extent of the lesions and to determine the quality of life respectively. The authors identified some key points on the activity of the tested cytokines on Psoriasis: low dose SKA cytokine administration is effective and safe and has a long-term action.

This feature may be crucial in view of the treatment of other chronic diseases such as vitiligo, an autoimmune dermatologic disorder characterized by skin depigmentation due to the loss of cutaneous melanocytes. In vitiligo an imbalance in cytokine expression at cutaneous lesions level is observed, probably caused by a shift of the immune system with a prevalence of Th1/Th17 (high IL-1 and IL-17 levels) and a reduction of the Tregs/Th2-driven response (low IL-4 level) TNF- α also has a pivotal role in oxidative stress-mediated cytotoxicity directed against melanocytes and keratinocytes [28,29]. Loss of melanocytes exerts a central role in Vitiligo depigmentation. Increased melanocytes death rate is due to the disruption of the cross-talk between these cells and keratinocytes.

Oxidative stress (free oxygen radicals) and other inflammatory triggers such as TNF- α induce keratinocytes apoptosis with consequent reduced production of keratinocytes-released factors SCF (Stem Cell Factor), ETs (Endothelins) and, above all, bFGF (basic Fibroblast Growth Factor) that negatively affects the vitality of melanocytes. Acting at the origin of the inflammatory phenomena counteracting pro-inflammatory cytokine with specific low dose SKA cytokines (IL-10, Anti-IL-1 and IL-4) and, in the meantime, stimulating melanocytes to produce melanin *via* up-regulation of trans-membrane receptors through SKA low dose b-FGF represent the new LDM approach for Vitiligo treatment.

3. Conclusions

The immune imbalance between the Th1/Th2/Th17-mediated cellular responses is a pivotal point in the etiology of numerous dermatologic disorders and the management of the altered cytokine profile could represent an important therapeutic approach.

Regrettably, if the intervention with high doses of recombinant cytokines, antibodies and other signal molecules is effective against some immune aspects of treated diseases on the other hand this approach is affected by unavoidable dose-dependent and time-dependent side effects; these pitfalls are particular important considering that autoimmune and inflammatory skin diseases are often chronic.

A new opportunity for the development of therapeutic strategies based on fine tuned immune rebalance interventions is allowed by the availability of medications containing low-dose SKA-activated cytokines. Data from pre-clinical research in the field of LDM and scientific evidences of LDM approach efficacy and safety in the treatment of Psoriasis Vulgaris and the well-grounded therapeutic hypothesis based on the administration of low dose SKA cytokines for

Vitiligo allow us to speculate that LDM-based therapeutic approach represents an unique opportunity for the development of an innovative immunological treatment for dermatological diseases characterized by an immune Th1/Th2/Th17 imbalance.

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