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New Frontiers in Vitiligo Treatment: The Low Dose Cytokines-Based Therapy

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Abstract

Skin depigmentation phenomena, caused by the loss of melanocytes, are the distinctive feature of vitiligo. The inner mechanisms of melanocyte loss are still unclear; however, an increasing number of basic and clinical observations highlighted the fundamental role of cellular immunity, chronic inflammatory phenomena and intercellular cross-talk breakdown in vitiligo pathogenesis.

The modulation of inflammatory phenomena and immune response and the restoration of keratinocytes-melanocytes axis with specific low dose SKA interleukins, antibodies and basic fibroblast growth factor represent an innovative therapeutic approach for vitiligo treatment based on Low Dose Medicine paradigm.

Keywords: Vitiligo; Low dose medicine; Inflammation; Sequential kinetic activation; Interleukin 4; Interleukin 10; Anti-interleukin-1 antibodies; Basic-fibroblast growth factor

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Introduction

Vitiligo: A skin disorder with a complex etiology

Vitiligo is a disease characterized by progressive skin depigmentation phenomena, mainly induced and maintained by the loss of melanocytes (or a reduction in its activity) at the cutaneous level. Vitiligo pathogenesis is very complex and the inner causes are still unclear but, in recent years, scientific research identified the altered immune response as one of the main cause of vitiligo onset and spreading.

A prevalent Th1/Th17 immune response characterizes vitiligo; high levels of Interleukin-1 (IL-1) are detected mainly at perilesional level, triggering local inflammatory response and oxidative stress phenomena in association with TNF-α [1,2]. Increased expression of IL-17 with concomitant low levels of IL-4 (impaired Th2 response) highlight the autoimmune picture of Vitiligo [3]. An alteration in anti-oxidative response is detected also in keratinocytes located in vitiligo lesional skin. The Protease-activated receptor-2 (PAR-2) enhances both inflammation and Nrf2-mediated response against oxidative stress at skin level PAR-2 activation promotes melanin uptake from keratinocytes and anti-oxidant enzymes expression (e.g: quinone oxidase, NQO-1, a phase II enzyme acting as ROS scavenger); both mechanisms are fundamental for cellular protection against oxidative triggers [4]. The breakdown of PAR-2/Nrf2 crosstalk is linked with the onset of skin diseases such Atopic Dermatitis and Vitiligo: in lesional keratinocytes, PAR-2 expression is impaired, resulting in reduced Nrf2 nuclear translocation and subsequent defective anti-oxidant response. In summary, decreased antioxidant enzymes activity and increased ROS levels, due to a chronic inflammatory condition driven by interleukin-2 (IL-2), seems to be linked with Nrf2 pathway alteration in vitiligo both in melanocytes and keratinocytes subsets. The cross-talk between keratinocytes and melanocytes is fundamental for the efficiency of the skin pigmentation mechanisms; basic-Fibroblast Growth Factor (b-FGF) is an important mediator produced and released by keratinocytes and targeting melanocytes, in fact, b-FGF promotes melanocytes growth, differentiation and melanin synthesis.

In vitiligo, the inflamed microenvironment and the increased oxidative stress are directly responsible of keratinocytes-melanocytes cross-talk breakdown [5,6]. These alterations in epidermal cellular composition and function, drive the depigmentation phenomena which represents the final expression of the Vitiligo etiopathogenetic pathway. b-FGF targets several cell types exerting a trophic action and regulating cellular proliferative mechanisms; these topics make it a suitable pharmacological molecule for the modulation of cellular growth, differentiation and migration phases. Recombinant b-FGF of bovine and human origin has been deeply tested evaluating its applicative uses as enhancer of bone repair and soft tissues lesion

healing by direct stimulation of fibroblasts. The dosages used in order to reach these goals are in the range of micrograms [7-9] and some related adverse effects, although not supported by statistical significance, are associated to the treatment with high doses of this growth factor. However, the dose-response ratio is not linear but reveals a typical bell-shaped curve fashion with a peak of activity in a concentration range identified between nanograms and picograms. Low Dose Medicine (LDM) for Vitiligo management: therapeutic efficacy of low dose SKA signaling molecules. In recent years, an innovative medical approach named Low Dose Medicine (LDM) arose. Low Dose Medicine was born from the merging of Molecular Biology with Psycho-Neuro-Endocrine-immunology (P.N.E.I.) [10,11], and was developed in recognition of research results in the field of the pharmacology of low doses [12-20]. Low Dose Medicine is a person-centered Medicine, based on three guiding principles:

• To treat the man and not just the disease.

• To act on the causes and not just the symptoms.

• To consider man as a whole mind-body and in his individuality.

Low Dose Medicine starts from an original idea in the medical field: to bring back a sick organism to the original physiological condition through the use of the same biological molecules normally present in the body and that, in healthy conditions, monitor and guide body functions. A critical point of signaling molecules (and peptides in general) oral administration is represented by their low bioavailability (typically less than 1-2%); an effective drug delivery system is requested in order to improve this key parameter. The use of physiological low doses (nanograms-picograms) per os in LDM is made possible by the application of SKA technique (Sequential Kinetic Activation is an innovative pharmaceutical production technique codified and standardized by GUNA S.p.a. Milan. Italy).

LDM approach gives the opportunity to design an innovative treatment for vitiligo based on the use of low doses of orally administered:

• SKA b-FGF in order to restore one of the most important melanocytes stimulating pathways.

• SKA interleukins and antibodies (IL-10, IL-4 and Anti-IL-1) in order to modulate inflammatory and oxidative stress phenomena.

Starting from this preliminary theoretical approach, Barygina V. and colleagues [21] evaluated the effects of low doses of SKA activated IL-4, IL-10, b-FGF, and beta-endorphin in the modulation of oxidative stress and on the proliferation of human keratinocytes. The researcher evaluated the effects of low dose SKA IL-4, IL-10, b-FGF, and beta-endorphin (10 fg/ml) in the modulation of intra- and extra-cellular oxidative stress and on the proliferation of human perilesional keratinocytes (PL) from skin samples of Vitiligo patients (*in vitro* study on cells obtained from lesion skin biopsies). The proved *in vitro* effectiveness of low dose SKA molecules against oxidative stress induced Lotti T. and colleagues [22] to perform a retrospective spontaneous clinical study comparing the effectiveness of current vitiligo treatments with the LDM-based therapeutic approach. In this study, data collected from differently treated patients were grouped and retrospectively evaluated (group 1: SKA b-FGF; group 2: SKA IL-4; IL-10; Anti IL-1; group 3: Narrow Band UVB; group 4: SKA b-FGF + Narrow Band UVB; group 5: SKA IL-4; IL-10; Anti IL-1 + Narrow Band UVB; group 6: topical betamethasone dipropionate group 7: SKA b-FGF + topical betamethasone dipropionate; group 8: SKA IL-4; IL-10; Anti IL-1 + topical betamethasone dipropionate; group 9: Ginko Biloba; group 10: sunlight exposure). The obtained results showed the ability of the low dose SKA treatments to reduce the depigmented skin surfaces and to block the spread of the lesions. The number of patients/group with a moderate (reduction of depigmentation in 25-50% of the affected area) to excellent (reduction of depigmentation in >75% of the affected area) response was globally considered as a positive result: low dose SKA b-FGF induced an improvement in 74% of patients and the association with low dose SKA IL-4, IL-10 and anti-IL-1 antibodies was effective in 77% of evaluated cases. The association of low dose SKA treatments with the topical UVB treatment resulted in the increase of positive outcome up to 92-93% paving the way to an integrated use of the two approaches. Low dose SKA signaling molecules efficacy and safety in Vitiligo treatment was also assessed, no adverse effects were reported.

Summary

In summary, the recently published preclinical and clinical study demonstrated:

• The efficacy of low doses of SKA signaling molecules in order to reduce oxidative damages.

• The ability of low dose SKA administered molecules to significantly reduce the depigmented skin surfaces and to block the spread of the lesions.

• The efficacy and safety of low dose SKA signaling molecules in the treatment of vitiligo were also assessed, no adverse effects were reported.

The availability of low dose SKA-activated cytokines and the LDM approach (validated by preclinical and clinical evidences in terms of efficacy and safety) [23] leads to postulate a new therapeutic approach based on systemic oral administration of low doses of SKA activated cytokines and growth factors, which represents an innovative strategy for the treatment of dermatological diseases characterized by an immune Th1/Th2 imbalance, chronic inflammatory and intercellular cross-talk breakdown phenomena such as vitiligo.

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