

New Winning Strategies for Vitiligo: The Low Dose Cytokines Therapy Approach

Torello Lotti[†], Tania Rivkina and Miroslava Kadurina

University of Rome "G.Marconi" Rome, Italy

[†]Corresponding author: Professor Torello Lotti, University of Rome "G.Marconi", Via Plinio, 44-00193 Rome, Italy, Tel +393286214588; Fax +390637725647; E-mail: professor@torelloLotti.it

Rec date: October 01, 2015; Acc date: December 05, 2015; Pub date: December 11, 2015

Copyright: © 2015 Lotti T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Vitiligo is a dermatologic pigmentary disorder triggered by melanocytes' loss and sustained by a deep immune imbalance which induce chronic inflammation and excessive oxidative stress phenomena at skin level. Current therapies are mainly symptomatic and designed in order to inhibit the inflammatory mediators at vitiligo patches level.

To restore the correct immune balance between Th1/Th17 and Th2/Treg response and concomitantly rebalancing the inflammatory response represents an innovative and effective approach for Vitiligo treatment; Low Dose Medicine theories and the availability of specific low dose SKA interleukins, antibodies and growth factors allows researchers and clinicians to act simultaneously against all the main etiologic causes of vitiligo and makes possible to design new therapeutic approaches for vitiligo.

Keywords: Vitiligo; Inflammation; Low dose medicine; Interleukin 4; Interleukin 10; Anti-interleukin-1 antibodies; Basic-fibroblast growth factor; Phototherapy; Narrow-band UVB

Introduction

Vitiligo is an inflammatory autoimmune skin disorder characterized by the progressive appearance of depigmented skin lesions caused by the loss of melanocytes at the cutaneous level. The global incidence of vitiligo is between 0.5% and 1% with peaks of 5/8% localized in Asiatic countries, especially in India, where it is considered a severe invalidating social stigma [1,2].

The etiology of vitiligo is still unclear but a growing number of observations have led the researchers to consider altered cellular immunity as a key factor of melanocyte loss [3]; a shift in the immune response, characterized by the prevalence of Th1/Th17-related cytokines (pro-inflammatory) instead of a Tregs/Th2-related one (anti-inflammatory), is responsible of the increase of proinflammatory cytokines primarily observed on the border of lesional and perilesional vitiliginous patches [4].

Interleukin-1 β ; Interleukin-6 and TNF- α , play a key role in inflammation and oxidative stress-enhanced cytotoxicity which impairs both melanocytes and keratinocytes survival [5-7].

Chronic inflammatory status, excessive oxidative stress and altered immune response induce the loss of cross-talk between keratinocytes and melanocytes, altering the homeostatic levels of involved specific cytokines and growth factors (Figure 1). The comprehension of the inner mechanisms of the intra- and intercellular signaling pathways is crucial to better understand the vitiligo etiopathology, in order to design new innovative and effective therapeutic protocols.

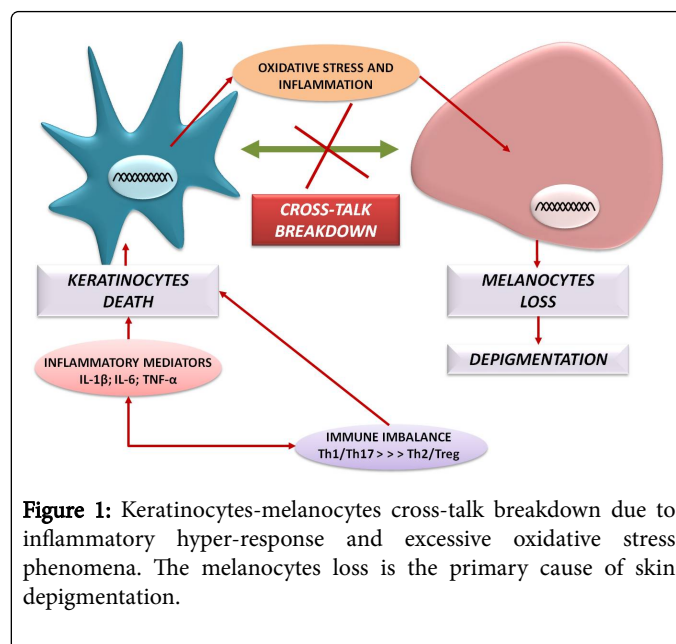


Figure 1: Keratinocytes-melanocytes cross-talk breakdown due to inflammatory hyper-response and excessive oxidative stress phenomena. The melanocytes loss is the primary cause of skin depigmentation.

Current Strategies for Vitiligo Treatment

The main goal of vitiligo treatment is to reduce the melanocytes' loss due to autoimmune response and to enhance their migration from surrounding normal skin to lesional patches.

Vitiligo therapeutic approaches are divided in pharmacological, physical and surgical categories (with the opportunity of combined therapies). Topical treatments realized with corticosteroids, calcineurin inhibitors and phototherapy represent the first line options for vitiligo [8].

Topical corticosteroids represent the first choice for vitiligo treatment; they are relatively cheap and easy to apply and are classified from low- to high-power corticosteroids.

Their use is limited by the risk of local adverse effects such as skin atrophy (due to collagen synthesis inhibition), telangiectasias, striae purpura and hypertrichosis. Systemic adverse effects are also present, the most severe are: adrenal axis ad growth inhibition, Cushing's Syndrome and muscular atrophy.

All the adverse effects are dose-dependent; high-power topic corticosteroids are indicated for the treatment of small vitiliginous patches for a brief period (2-4 months); low-power corticosteroids or other immunomodulators are second choice drugs which can be considered in order to decrease the risk of adverse events. The absence of clinical response within 3/4 months of treatment leads to the suspension of corticosteroid-based treatment [8,9].

Calcineurin inhibitors, which includes cyclosporine (not for topic use), pimecrolimus and tacrolimus, were originally studied and applied as immune suppressor agents in transplanted patients.

Unlike topical corticosteroids, calcineurin inhibitors do not brake the production of collagen and thus not lead to atrophy of the skin. For example, tacrolimus acts by inhibiting the production of pro-inflammatory cytokines by T lymphocytes through the block of IL-2 gene transcription; blocking the expansion of cytotoxic T lymphocytes, tacrolimus reduces the inflammatory and oxidative stress phenomena at the vitiligo patches level of injury resulting in skin repigmentation.

Both tacrolimus and pimecrolimus induce redness and itching of the skin but are generally more tolerated than corticosteroids [8,9].

Ultraviolet radiation (UV) of both A and B spectrum is used in the treatment of vitiligo; the action mechanism of UV rays is not fully understood but probably acts inducing immunosuppression and consequent reduction of melanocytes loss.

UVA phototherapy was first introduced in 1948 in combination with psoralens (PUVA therapy), the role of psoralens is to sensitize the skin to UVA rays improving their efficacy. Short-term (skin irritation, ocular/cutaneous phototoxicities, nausea and headache) and long-term (increased risk of skin cancer) side effects are linked with UVA/PUVA treatments [8-11].

In the last two decades Narrow Band UVB therapy arose. UVB-NB are effective and safe ensuring a higher repigmentation response compared to PUVA. UVB-NB treatment dispenses the use of psoralens avoiding the onset of gastrointestinal and ocular side effects [12,13].

Vitiligo topical treatments with pharmacologic or physical agents are effective but present some pitfalls such as highly variable response/repigmentation rates, low compliance (particularly in pediatric use) and quite severe side effects which make difficult the adherence to a long-term therapy.

Searching for New Therapeutic Opportunity for Vitiligo: The Low Dose Medicine

In recent years, preclinical and clinical results obtained by researchers operating in the field of Low Dose Medicine (LDM, an innovative medical approach based on Molecular Biology and Psycho-Neuro-Endocrine-Immunology (P.N.E.I.) and developed thanks to the results of research in the field of low doses pharmacology) highlighted the possibility of the treatment of Vitiligo using low dose activated

interleukins, antibodies, neuropeptides and growth factors (low dose SKA molecules) [14-22].

Immune imbalance, inflammation and consequent reduction of melanocytes' number and viability are the key triggers of skin depigmentation in vitiligo.

Acting at the origin of the altered inflammatory response (rebalance of pro-and anti-inflammatory mediators) with low dose SKA cytokines and antibodies (IL-10, IL-4 and Anti-IL-1) and, simultaneously, stimulation of melanocytes growth and melanin synthesis with low dose SKA basic-Fibroblast Growth Factor, represents the new LDM therapeutic approach for vitiligo.

Both basic and clinical studies were performed in order to test and validate the LDM approach for vitiligo.

In vitro/ex vivo experiments were conducted on human perilesional keratinocytes from skin of vitiligo patients (cells obtained from lesion skin biopsies) treated with low dose SKA IL-4, IL-10, b-FGF, and β -endorphin [20].

Obtained results highlighted a significant reduction of both intra-cellular and extra-cellular oxidative stress in cells treated with low dose SKA molecules. The improvement of oxidative status results in a reduction of inflammatory mediators with consequent increase of keratinocytes viability compared to control perilesional cells. These results validated the theoretical LDM approach confirming the key role of inflammation and oxidative stress phenomena in vitiligo onset and the correctness of the used low dose SKA molecules.

Furthermore, a retrospective spontaneous clinical study was performed and published by Lotti et al. [21].

In this retrospective study, repigmentation rate was evaluated in patients who received both pharmacological (corticosteroid cream), physical (Narrow Band UVB and sunlight exposure) topical treatments and systemic treatment (oral intake of *Ginkgo biloba* extract); additionally, some patients concomitantly assumed (systemic oral administration) low dose SKA IL-4; IL-10; Anti-IL-1 antibodies and low dose SKA b-FGF.

Evaluated clinical evidences highlighted that low dose SKA b-FGF alone and the association of low dose SKA IL-4, IL-10 and anti-IL-1 antibodies was effective in a significative number of cases with good repigmentation rates.

The association of low dose SKA treatments with the topical Narrow Band UVB treatment further boosted the repigmentation rate, paving the way to an integrated use of the two therapeutic tools.

Conclusions

In summary the efficacy of low doses of SKA signaling molecules in order to reduce oxidative damages was assessed with both preclinical and clinical studies with strong evidences of positive rebalancing action on inflammation, immune alterations and oxidative stress-induced cytotoxicity, the most important inflammatory triggers in Vitiligo. Low dose SKA signaling molecules safety was also assessed since no adverse effects were reported.

LDM approach, characterized by high compliance due to the simplicity of administration of oral drops and proven efficacy and safety, represent a valid supportive and/or alternative treatment to the currently applied therapeutic protocols for vitiligo [23].

In a “therapeutic overlapping” perspective, the insertion of LDM treatment in parallel with the standardized treatment protocol, offers the opportunity to gradually reduce the use of synthetic drugs with improved compliance and reduction of adverse effects; the LDM approach can be also useful in case of impossible, inadvisable or ineffective classic therapeutic intervention.

References

1. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N (2015) Vitiligo. *Lancet* 386: 74-84.
2. Pahwa P, Mehta M, Khaitan BK, Sharma VK, Ramam M (2013) The psychosocial impact of vitiligo in Indian patients. *Indian J Dermatol Venereol Leprol* 79: 679-685.
3. Sandoval-Cruz M, García-Carrasco M, Sánchez-Porras R, Mendoza-Pinto C, Jiménez-Hernández M, et al. (2011) Immunopathogenesis of vitiligo. *Autoimmun Rev* 12: 762-765.
4. Wang CQ, Cruz-Inigo AE, Fuentes-Duculan J, Moussai D, Gulati N, et al. (2011) Th17 cells and activated dendritic cells are increased in vitiligo lesions. *PLoS One* 6: e18907.
5. Tu CX, Gu JS, Lin XR (2003) Increased interleukin-6 and granulocyte-macrophage colony stimulating factor levels in the sera of patients with non-segmental vitiligo. *J Dermatol Sci* 31: 73-78.
6. Li P, Ma H, Han D, Mou K (2015) Interleukin-33 affects cytokine production by keratinocytes in vitiligo. *Clin Exp Dermatol* 40: 163-170.
7. Webb KC, Tung R, Winterfield LS, Gottlieb AB, Eby JM, et al. (2015) Tumour necrosis factor- α inhibition can stabilize disease in progressive vitiligo. *Br J Dermatol* 173: 641-650.
8. Faria AR, Tarlé RG, Dellatorre G, Mira MT, Castro CC (2014) Vitiligo--Part 2--classification, histopathology and treatment. *An Bras Dermatol* 89: 784-790.
9. Speeckaert R, Speeckaert MM, van Geel N (2015) Why treatments do(n't) work in vitiligo: An autoinflammatory perspective. *Autoimmun Rev* 14: 332-340.
10. Shenoi SD, Prabhu S (2014) Photochemotherapy (PUVA) in psoriasis and vitiligo. *Indian J Dermatol Venereol Leprol* 80: 497-504.
11. Tippisetty S, Goudi D, Mohammed AW, Jahan P (2013) Repair efficiency and PUVA therapeutic response variation in patients with vitiligo. *Toxicol In Vitro* 27: 438-440.
12. Sapam R, Agrawal S, Dhali TK (2012) Systemic PUVA vs. narrowband UVB in the treatment of vitiligo: a randomized controlled study. *Int J Dermatol* 51: 1107-1115.
13. Xiao BH, Wu Y, Sun Y, Chen HD, Gao XH (2015) Treatment of vitiligo with NB-UVB: A systematic review. *J Dermatolog Treat*. 26: 340-346.
14. Gariboldi S, Palazzo M, Zanobbio L, Dusio GF, Mauro V, et al. (2009) Low dose oral administration of cytokines for treatment of allergic asthma. *Pulm Pharmacol Ther* 22: 497-510.
15. D'Amico L, Ruffini E, Ferracini R, Roato I (2012) Low Dose of IL-12 stimulates T Cell response in cultures of PBMCs derived from Non Small Cell Lung Cancer Patients. *Journal of Cancer Therapy* 3: 337-342.
16. Cardani D, Dusio GF, Luchini P, Sciarabba M, Solimene U, et al. (2013) Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation. *Gastroenterology Research* 6: 124-133.
17. Radice E, Miranda V, Bellone G (2014) Low-doses of sequential-kinetic-activated interferon-gamma enhance the ex vivo cytotoxicity of peripheral blood natural killer cells from patients with early-stage colorectal cancer. A preliminary study. *Immunopharm* 19: 66-73.
18. Roberti ML, Ricottini L, Capponi A, Sclauzero E, Vicenti P, et al. (2014) Immunomodulating treatment with low dose Interleukin-4, Interleukin-10 and Interleukin-11 in psoriasis vulgaris. *J Biol Regul Homeost Agents* 28: 133-139.
19. Luchetti P (2014) Observational pilot study on the increasing of visual function in patients with retinal atrophy treated with drugs of Low Dose Medicine. *Minerva Oftalmologica* 56: 53-61.
20. Barygina V, Becatti M, Lotti T, Moretti S, Taddei N, et al. (2015) Treatment with low-dose cytokines reduces oxidative-mediated injury in perilesional keratinocytes from vitiligo skin, *Journal of Dermatological Science*. *J Dermatol Sci* 79: 163-170.
21. Lotti T, Hercogova J, Wollina U, Chokoeva AA, Zarrab Z, et al. (2015) Vitiligo: successful combination treatment based on oral low dose cytokines and different topical treatments. *J Biol Regul Homeost Agents* 29: 53-58.
22. Radice E, Bellone G, Miranda V (2015) Enhancement of the Immunostimulatory Functions of Ex Vivo-Generated Dendritic Cells from Early-Stage Colon Cancer Patients by Consecutive Exposure to Low Doses of Sequential-Kinetic-Activated IL-4 and IL-12. A Preliminary Study. *Transl Oncol* 8: 327-338.
23. Lotti T, Hercogova J, Fabrizi G (2015) Advances in the treatment options for vitiligo: activated low-dose cytokines-based therapy. *Expert Opin Pharmacother* 16: 2485-2496.