



# **OVERVIEW OF VITILIGO RESEARCH**

**July- September 2014**

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- Markedly reduced risk of melanoma and non-melanoma skin cancers was revealed in a study of large cohort of vitiligo patients.
- Epigallocatechin-3-gallate (EGCG), a green tea catechin with antioxidative properties, emerges as a potential preventive treatment for vitiligo.
- Results of Phase I clinical trial of afamelanotide showed that experimental treatment might be useful in treatment of vitiligo, especially in dark-skinned individuals
- Narrow-band ultraviolet B phototherapy is superior over oral minocycline in arresting vitiligo progression.
- Adipose-derived stem cells might improve efficiency of melanocyte transplantation in vitiligo treatment.
- Interleukin-33 emerges a possible player in vitiligo pathogenesis

This is a review of research results in the vitiligo field which were indexed in the PubMed database ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)) for the period from July 2014 till September 2014. Abstracts of papers were retrieved from the PubMed database using the search term “vitiligo” with a filter set up to retrieve records with *creation date* between July 01, 2014 and September 30, 2014. Retrieved records were manually checked for a relevance to and significance for the field of vitiligo research. Fifty nine records were found to be relevant and of interest, and were included into this quarterly overview.



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## Reviews & Comments

Faria and co-authors [PubMed](#) published the second part of a review series on vitiligo covering disease classification, histopathology and treatments. Czajkowski and coauthors [PubMed](#) summarized the current state in the genetic research of vitiligo. Lotti et al. [PubMed](#) summarized the role of neuropeptides in a control of regional immunity in a projection on inflammatory skin diseases including vitiligo, and published an update on the psycho-neuro-endocrine-immune connection in vitiligo. [PubMed](#) Lee & Fisher [PubMed](#) published a review devoted to melanocyte stem cells, with a discussion of their possible use in controlling skin pigmentary disorders. Xiao et al. [PubMed](#) reported results of a systematic review of vitiligo treatment with narrow-band ultraviolet B (NB-UVB), with the conclusion on similar efficiency compared to excimer laser, excimer lamp and PUVA therapy, with acceptable side effects. Zhang et al. [PubMed](#) presented a review of non-surgical treatments for vitiligo. Silverberg [PubMed](#) overviewed recent advances in childhood vitiligo. Finally, Allam & Riad [PubMed](#) provided a review on vitiligo, covering disease pathogenesis and existing treatment options.

Seneschal et al. [PubMed](#) commented on the approach suggested by Webb et al. [PubMed](#) for increasing efficiency and accelerating depigmentation in patients with extensive vitiligo. Authors highlight the need to closely investigate side effects, in particular, induction of undesired autoimmunity, of the approach consisting of inclusion of immune adjuvants to boost anti-melanocyte immune response induced by locally applied bleaching agents.

Qui et al. [PubMed](#) commented the work of Jian et al. [PubMed](#) on impaired activation of the Nrf2-ARE signaling pathway in vitiligo melanocytes, which undermines oxidative stress response and might be a possible mechanism for melanocyte degeneration in vitiligo. In view of the revealed molecular mechanism, the authors suggest that the Nrf2-ARE pathway could be exploited as a target for preventive or therapeutic interventions for vitiligo.

## Disease Management And Clinical Features

Ezzedine et al. [PubMed](#) conducted a retrospective multi-center evaluation study aiming to delineate hypochromic vitiligo. As a result of analysis of 24 cases, hypochromic vitiligo, which is not yet a part of vitiligo classification, was found to be associated predominantly with darker skin types.

Paradisi and colleagues [PubMed](#) in a large (10040 patients) study ultimately confirmed previously existing opinion on reduced risk of developing melanoma and non-melanoma



skin cancers, despite frequently elevated levels of ultraviolet exposure due to vitiligo treatment.

Kim et al. [PubMed](#) addressed the question of tractability of facial childhood vitiligo, with 9% of non-responders revealed and more than 42% with excellent results of treatment. Although the number of treated by epidermal grafting patients was low (12 patients), this treatment modality seems to be a good option for childhood vitiligo treatment with excellent results.

Jung et al. [PubMed](#) reported results of an analysis of skin thickness in vitiligo, with the conclusion on thicker epidermis in lesional skin, especially on sun-exposed areas, which might reflect a compensatory response to a lack of pigmentation.

## Epidemiology

Vora et al. [PubMed](#) reported clinical characteristics of 1010 Indian vitiligo patients confirming existing epidemiological features of vitiligo.

Erfan et al. [PubMed](#) analyzed temperaments and character profiles in first-onset vitiligo and alopecia areata. While no deviation from the normal population was seen for alopecia areata, distinct temperament was observed for vitiligo patients (being unenthusiastic and unemotional), as well as character profile (worry and pessimism), independent of their psychiatric comorbidities.

Silverberg et al. [PubMed](#) studied regional variations and association of birthplace with vitiligo extent. The analysis revealed significant variations of this parameter in the US thus suggesting that there are unrecognized environmental risk factors for vitiligo.

Dogan et al. [PubMed](#) found that Turkish vitiligo patients are characterized by increased rates of positivity for *Helicobacter pylori*, its virulence factor CagA and *H. pylori* antibodies. Future studies are warranted to explain the revealed relationship.

## Comorbidities

Thyroiditis has been repeatedly reported as the main vitiligo comorbidity. In two studies (Yang et al. [PubMed](#) and Colucci et al. [PubMed](#)), in agreement with this, increased incidence of thyroid autoantibodies was found.

Hearing dysfunction comorbid to vitiligo remains a controversial issue. Results of a study by Anbar et al. [PubMed](#) add to the existence of this comorbidity as 60.3% out of 53 vitiligo patients had bilateral cochlear dysfunction. Interestingly, no difference in cochlear dysfunction has been observed between segmental and non-segmental vitiligo.



## Quality of life (QoL)

Ramien et al. [PubMed](#) provide evidence of impaired QoL in children and teenagers with visible vascular and pigmentary anomalies, including vitiligo, which can be improved by the use of cosmetic camouflage.

Mishra et al. [PubMed](#) assessed QoL of Indian vitiligo patients with the DLQI tool, with the expected finding that vitiligo affects the QoL of the majority (84%) of vitiligo patients. A similar conclusion was made by Ramakrishna & Rajni, [PubMed](#) highlighting the role of mental health professionals in management of vitiligo patients.

Amer and colleagues [PubMed](#) showed that vitiligo affects not only patient QoL, but, in childhood vitiligo, it also has an impact on the parent's who, as revealed, have significant psychological problems, thus signifying importance of attention not only to children with vitiligo but also to their parents.

## Vitiligo triggers

Serra et al. [PubMed](#) reported another case of vitiligo-like depigmentation induced by topically applied imiquimod.

Mavilia & Mercuri [PubMed](#) reported a case of Nd:YAG laser induced vitiligo in a patient with a history of Sutton nevus.

Koroda et al. [PubMed](#) investigated the depigmentation capacity of 4-(4-hydroxyphenyl)-2-butanol (HPB) using a guinea pig model. HPB application induced depigmentation, which was accompanied by melanocyte loss. However, termination of HPB application resulted in spontaneous repigmentation indicating that HPB likely to have a direct toxic effect on melanocytes rather than induce an immune response to them.

Vajrala et al. [PubMed](#) reported a rare case of vitiligo induction at the site of radiotherapy, with the subsequent progression of the disease to generalized form.

## Case reports

Shin et al. [PubMed](#) reported a case of pre-existing segmental vitiligo which recurred after immunotherapy with house dust mites. This case suggests that segmental vitiligo, similarly to non-segmental one, can have an autoimmune background.

Joo et al. [PubMed](#) reported a case of vitiligo improvement after hydroxychloroquine treatment of a patient with rheumatoid arthritis. Owing to immunosuppressive and anti-inflammatory mechanisms of hydroxychloroquine action, this case highlights immune system-related nature of vitiligo.



Ashok et al. [PubMed](#) described a case of gingival vitiligo accompanied by review of the literature on this matter.

## Understanding mechanisms of vitiligo pathogenesis

Li et al. [PubMed](#) studied expression of IL-33 in vitiligo patients. They found that both IL-33 and its receptor are over-expressed in lesional skin. In addition, vitiligo patients have increased serum level of IL-33. Finally, keratinocyte-derived IL-33 induced secretion of IL-6 and TNF $\alpha$  and decreased SCF production. Results of this study point to IL-33 as to a novel player in vitiligo pathogenesis.

## Genetic studies

Laddha et al. [PubMed](#) investigated relation of genetic variations in *NPY* and *IL1B* genes with vitiligo susceptibility in a case-controlled study on the Gujarat population (about 500 cases and 1000 controls). Results of the study revealed existence of a link between assayed genetic variations and vitiligo. Interestingly, increased level of *NPY* has been previously documented in vitiligo patients with the suggestion on its role in vitiligo pathogenesis. [PubMed](#) Interestingly, there was moderate correlation between variation in *IL1B* gene promoter and *IL1B* transcript level in blood cells suggesting a functional link between the genetic variation and immune-system associated processes.

Jang et al., [PubMed](#) using whole-genome resequencing, reported identification of genetic variations in Smyth line chicken, a well-known spontaneous vitiligo model, which might determine vitiligo susceptibility. Results of the study would definitely contribute to understanding of genetic components responsible for vitiligo onset and progression.

He et al. [PubMed](#) published results of meta-analysis showing no correlation between 389 C>T polymorphism in catalase *CAT* gene and vitiligo susceptibility, although the authors do not exclude existence of effect through gene-gene and gene-environment interactions, which should be addressed in large primary studies.

## Candidate biomarkers

Along with the genetic study, Laddha et al. [PubMed](#) found elevated level of *IL1B* transcript in blood of vitiligo patients compared to controls, which was even more pronounced in patients with active disease.

Beheshti et al. [PubMed](#) evaluated vitamin D level in 100 Iranian vitiligo patients, with the finding on its lower than normal level. At the same time, Ustun et al. [PubMed](#) found no difference in vitamin D level between Turkish vitiligo patients and healthy controls, although in both groups it was low. Akin, Sehwat et al. [PubMed](#) also found prevailing vitamin D deficiency and insufficiency in vitiligo patients, with also lower than normal level in all control subjects. However, in this study, vitamin D level in vitiligo patients was lower

than in controls. NB-UVB phototherapy resulted in improvement of vitamin D level, however with a moderate correlation with treatment success.

Teulings et al. [PubMed](#) investigated immunological differences between vitiligo and leukoderma associated with melanoma. Although Mart-1 is a vitiligo-related antigen, and the respective cytotoxic T-cells were repeatedly detected in vitiligo patients, vitiligo, unlike melanoma-associated leukoderma, is characterized by a lack of humoral response against Mart-1, which is in line with previous findings. [PubMed](#) Thus, presence of Mart-1 antibodies in vitiligo might be used as a marker of melanoma-associated vitiligo.

## Mechanisms of treatments

Al-Shobaili & Rasheed [PubMed](#) addressed the question of immune response against ONOO-modified mitochondrial DNA in vitiligo patients, and found evidence of it, as well as signs of nitrosative stress in general in patients with long disease duration. These findings prompt further investigation of potential role of nitrosative stress in vitiligo pathogenesis.

Huang et al. [PubMed](#) investigated effects of tacrolimus in a model of A375 melanoma cells. The results obtained suggest that tacrolimus might stimulate melanogenesis and enhance cell migration, which is a pre-requisite for repigmentation in vitiligo treatment.

Kawakami et al. continued investigation of 1,25-dihydroxyvitamin D3 action on melanogenesis. In their study, [PubMed](#) 1,25-dihydroxyvitamin D3 decreased proliferation of cultured human melanocytes and melanoblasts, and increased tyrosinase activity. In the epidermis, 1,25-dihydroxyvitamin D3 exposure resulted in increased melanogenesis and increased expression of endothelin B receptor on epidermal melanoblasts. Authors suggest, that stimulation of endothelin B receptor expression could be a mechanism explaining effect of 1,25-dihydroxyvitamin D3 on melanogenesis.

Kovacs et al. [PubMed](#) characterized melanocytes in repigmented skin after punch grafting, with the results suggesting that intergraft repigmentation is due to activation of donor melanocytes.

Yazdani and coauthors [PubMed](#) summarized known mechanisms of NB-UVB in combination with other therapies in treatment of vitiligo.

## Methodological advancements

Kaliyadan & Ashique [PubMed](#) suggested optimization of targeted phototherapy of vitiligo in patients with type I-II skin by prior marking lesion boundaries under Wood's lamp to precisely and completely target lesions.

Machado Filho & Timoner [PubMed](#) described an epidermal curettage technique for tissue harvesting from donor site for autologous grafting in vitiligo. The technique is simple



compared to other methods of obtaining material for grafting, and has been successfully used for long time in the author's service.

Ashique & Srinivas<sup>[PubMed](#)</sup> suggested the technique allowing for simplified handling of blister roof grafts and their manipulation, including cutting.

## Novel treatment modalities

Lim et al.<sup>[PubMed](#)</sup> studied efficiency of transplantation of melanocytes mixed or co-cultured with human adipose-derived stem cells. In animal models, the procedure was found to be equally as safe as transplantation of melanocytes alone, with better efficiency observed when melanocytes were transplanted with adipose-derived stem cells.

Zhu et al.<sup>[PubMed](#)</sup> investigated effect of epigallocatechin-3-gallate (EGCG), a green tea catechin with antioxidative properties, in a model of monobenzene-induced vitiligo in mice. Uptake of EGCG delayed vitiligo onset and prevalence as well as decreased depigmentation area. Importantly, EGCG uptake also decreased perilesional accumulation of CD8+ T-cells and lowered serum TNF $\alpha$ , IFN $\gamma$  and IL-6, cytokines likely to be involved in vitiligo pathogenesis. Therefore, EGCG emerges as a potential preventive treatment for vitiligo.

*Nigella sativa* extract is known to possess melanogenic properties.<sup>[PubMed](#)</sup> Ghorbanibirgani and coauthors<sup>[PubMed](#)</sup> compared effects of topical *N. sativa* oil and fish oil on repigmentation in vitiligo patients. Both treatments resulted in improvement of VASI score but the improvement was more pronounced for *N. sativa* oil. Based on the results, authors suggest use *N. sativa* oil in combination with other therapies in vitiligo treatment.

## Clinical studies and trials

Lim and coauthors<sup>[PubMed](#)</sup> reported results of multicenter phase I clinical trial of afamelanotide, an  $\alpha$ -melanocyte-stimulating hormone analogue, in combination with NB-UVB. Authors noticed faster repigmentation in experimental group (28 subjects) compared to the control group (27 subjects) receiving only NB-UVB. Authors also observed better repigmentation in the experimental group, yet this effect was limited to dark skin types (type IV-VI) but not for type III skin.

Siadat et al.<sup>[PubMed](#)</sup> compared efficiency of 3-month treatment with NB-UVB or oral minocycline in arresting vitiligo progression. Result of the study on 42 patients with 1-year follow-up showed that NB-UVB is superior over minocycline in arresting vitiligo progression (76% versus 33%).

Khullar et al.<sup>[PubMed](#)</sup> found no benefit of adding topical calcipotriol to NB-UVB phototherapy in vitiligo treatment in a right-left comparative study on 27 patients. This result is in line with the majority of previous reports on lack of topical vitamin D analogue effects on repigmentation when combined with phototherapy.



Mattin et al. [PubMed](#) compared efficiencies of 308 nm excimer laser alone or in combination with tacrolimus in a retrospective study. The results showed that combinatorial treatment has significantly better efficiency, with almost 50% of cases having more than 75% of repigmentation compared to 8% in the monotherapy group.

Wang et al. [PubMed](#) studied effect of intralesional corticosteroid (triamcinolone acetonide) injection on repigmentation. The observed efficiency (study cohort of 9 patients) was high (all patients responded, with repigmentation of 80%-90%). Authors suggest that this treatment option can be easily introduced into practice, yet additional clinical studies are required to prove its efficiency. However, previous a study of Vasistha & Singh [PubMed](#) revealed no difference between injections of steroids or water, thus potentially attributing the observed repigmentation to needling rather than to the specific action of the drug.

Shan et al. [PubMed](#) reported results of the first-in-China clinical trial of use-at-home NB-UVB device for treatment of vitiligo. Data obtained on a cohort of 93 patients indicate good compliance of patients and good efficiency of repigmentation (73.1% achieved more than 50% repigmentation, among them 37.6% - more than 75% repigmentation). Based on author's observations, lack of induction of repigmentation after 3 month of the treatment is an indication for treatment discontinuation. Importantly, a locally produced NB-UVB hand-held lamp was used in the study, the affordable price of which would facilitate widespread dissemination of the method among vitiligo patients.

Naini and coauthors [PubMed](#) studied efficiency of a cream containing pseudocatalase/superoxide dismutase in a right-left comparative study (23 patients). Authors found no difference between the investigated cream and the placebo, thus further adding evidence to a lack of effect of topical formulations containing pseudocatalase and/or superoxide dismutase on repigmentation in vitiligo.

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