OVERVIEW OF VITILIGO RESEARCH

January – March 2015

Contents

- CCL22 molecule which promotes regulatory T-cell homing to skin emerges as a candidate for rational-based vitiligo therapy development
- Intrinsic defects in melanocyte cell adhesion secured by E-cadherin protein might be a factor predisposing to vitiligo
- CO_2 laser combined with topical betamethasone and narrow-band ultraviolet B can be an efficient treatment option of vitiligo in hard-to-repigment locations
- Involvement of Th17 cells in vitiligo pathogenesis is getting more experimental support
- A case of vitiligo onset apparently caused by atomoxetine, a drug used to treat attention deficit/hyperactivity disorder, has been documented
- Two studies confirmed that vitiligo onset in melanoma patients is a good prognostic factor of melanoma treatment success likely witnessing successful activation of anti-tumor immunity

This is a review of research results in the vitiligo field which were indexed in the PubMed database (www.ncbi.nlm.nih.gov/pubmed) for the period from January 2015 till March 2015. 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 January 01, 2015 and March 31, 2015. 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 in this quarterly overview.

Reviews & Comments

Matin[PubMed] presented results of analysis of relative efficiency and safety of various surgical interventions for vitiligo in adults and children. Mohammed et al.[PubMed] published a review focused on current state of understanding of vitiligo pathogenesis. Whitton et al.[PubMed] analyzed and summarized results on interventions for vitiligo assessed in randomized controlled trials as an update of published in 2010 Cochrane review. In conclusion, authors point on difference in study designs and outcome measurements, the need of high-quality randomized clinical trials, assessment of permanence of repigmentation and addressing QoL issue. Sarnoff published brief overview of available treatments for vitiligo.[PubMed] Ezzerdine et al.[PubMed] emphasized that distinguishing between segmental and nonsegmental forms of vitiligo is an important issue in selection of appropriate treatment, along with importance of early-after-onset treatment of vitiligo and profound psychosocial effect of the condition. Choi et al.[PubMed] reviewed emerging potential uses of prostaglandin F2α analogues, which has been successfully tested in vitligo treatment. Ghafourian et al.[PubMed] published a review on vitiligo covering mechanisms of pathogenesis and currently used treatment modalities, with the suggestion that traditional Chinese medicine could bring improvement in vitiligo treatment.

Kohli et al.[PubMed] published comment on recently appeared manuscript on vitiligo assessment methods.[PubMed]

Disease Management And Clinical Features

Sharma[PubMed] commented the work of Ezzerdine et al.[PubMed] appeared online in 2014, highlighting a need for a deeper study of hypochromic vitiligo, which might be misdiagnosed due to its, for vitiligo, unusual clinical presentation.

Tolkachjov & Comfere[PubMed] noticed that vitiligo can be clinically mimicked by hypopigmented mycosis fungoides, a rare variant of cutaneous T-cell lymphoma, with the need of biopsy for proper diagnosis.

Epidemiology

Abraham & Raghavan[PubMed] conducted a study which showed generally low adherence of vitiligo patients to a treatment, and analyzed factors affecting adherence.

Nagarajan et al.[PubMed] addressed the prevalence of oral manifestation of vitiligo among vitiligo patients, with 55 out of 100 examined patients having depigmentation in oral cavity (lip being the most common site).

Comorbidities

Yazdanpanah et al.[PubMed] analyzed the incidence of psoriasis, vitiligo and their simultaneous occurrence among 6200 dermatological clinic patients. Based on the data obtained, authors found increased incidence of vitiligo among psoriasis patients, and vice versa, thus suggesting common factors and mechanisms contributing to these diseases.

Tatli et al.[PubMed] reported that development of vitiligo might be a good prognostic

factor in melanoma treatment with temozolomide. Along with that, Teuling and coauthors[PubMed] noted that although vitiligo development is a rare case in melanoma patients treated with immunotherapy, its development is an indicator of robust anti-melanoma immunity and is associated with improved treatment outcome.

Dash et al.[PubMed] assayed frequency of anti-thyroid antibodies in vitiligo patients without symptoms of thyroid disease. The observed frequency was 28%, which in authors' opinion warrant screening of vitiligo patients for anti-thyroid antibodies.

Herrmann et al.[PubMed] analyzed factors predisposing mycosis fungoides patients to vitiligo, among which methotrexate and CD4 antibody therapy were found to be associated with increased risk of vitiligo. At the same time, decreased risk was associated with PUVA (psoralen plus ultraviolet A) therapy and nitrogene mustard use, both of which are also used in vitiligo treatment. However, authors suggest that multiple factors may contribute to vitiligo onset, and those might be patient-specific.

Guengoer et al.[PubMed] reported that vitiligo patients are characterized by decreased tear production, especially in case of acrofacial vitiligo, yet the significance and impact of this finding should be further confirmed and explored.

Quality of life (QoL)

Sangma et al.[PubMed] assessed quality of life and psychological morbidity in vitiligo patients with an expected finding of increased Dermatology Life Quality Index (DLQI) scoring indicating impaired QoL, as well as more depression compared to healthy control group.

Al-Shobailli[PubMed] reported that excimer laser treatment improves QoL of vitiligo patients, with the conclusion on the feasibility of excimer laser treatment for patients with multiple focal lesions, even if some of them will fail to show significant clinical improvement.

The study of Sarhan et al.[PubMed] revealed a negative correlation between Vitiligo Area Scoring Index (VASI) and sexual satisfaction of women affected by vitiligo, thus advising sexual and psychological assessment of vitiligo patient to improve outcomes and increase patients' compliance.

Vitiligo triggers

Bilgic & Bilgic[PubMed] reported a case of vitiligo onset after initiation of atomoxetine for attention deficit/hyperactivity disorder. Atomoxetine is an inhibitor of norepinerphine reuptake which intimately might provide a link to neuroendocrine theory of vitiligo pathogenesis.

Rifaioglu et al.[PubMed] assessed the frequency of *Helicobacter piroli* infection on a small (34 individuals) cohort of vitiligo patients, with the finding of increased frequency of infection by the pathogene. While the size of study cohorts poses these results as a preliminary, these findings might hint on *Helicobacter piroli* as on the entity contributing to vitiligo triggering, which significance should be estimated in future large-scale studies.

Dated back to 2013, Saeedlo & Shariat[PubMe] repoted a case of vitiligo induction in a patient with bipolar disorder after switching from valproate to carbamazepine. After canceling the drug, depigmentation has been gradually decreased but, intriguingly, later prescribed carbamazepine did not caused depigmentation.

Case reports

Garner et al.PubMed reported a case of vitiligo after treatment of chronic cheilitis with isotretinoin, with a hypothesis of cheilitis-mimiced koebnerization as a trigger.

Khandalavala & NirmarajPubMed reported a case of rapid partial repigmentation in vitiligo patient in response to gluten-free diet, thus potentially pointing on the role of diet in vitiligo, most likely – in otherwise susceptible to vitiligo individuals, especially those suffering from celiac disease, an encountered comorbid to vitiligo condition.

Understanding mechanisms of vitiligo pathogenesis

Wang et al.PubMed showed that intracellular double-strand RNA (dsRNA) mimicking viral dsRNA induces melanocyte cell death accompanied by induction of pro-inflammatory interferon β, TNFα, interleukin-6 and -8 cytokines. These findings might be relevant to previously suggested but currently poorly experimentally supported viral hypothesis of vitiligo pathogenesis (editorial comment on this work by Boniface et al.PubMed appeared in *Experimental Dermatology* journal).

Tembhre et al.PubMed analyzed a role of T-cell immunoglobulin- and mucin-domain-containing molecule-3 (TIM-3) in vitiligo. Authors reported increased frequency of TIM3-positive $CD4^+$ T-cells in peripheral blood of subjects with active generalized vitiligo which was correlated with body surface area involvement. In addition, increased expression of TIM-3 and its ligand, galectin-9, was found in both peripheral blood and lesional/perilesional skin of these subjects. These findings suggest that TIM-3/galectin-9 signaling, which is commonly suppressive for T-cell functions, can play a role in vitiligo development and spreading.

Zedan et al.PubMed added another piece of evidence to oxidative stress presence in vitiligo patients with their findings on decreased glutathione peroxidase level. Along with that, AgrawalPubMed reported that malondealdehyde level is increased while catalase level is decreased in vitiligo patients, which is in line with previous reports and further confirms existence of systemic oxidative stress in vitiligo patients.

Previously, interferone γ (IFNγ) has been implicated in vitiligo pathogenesis. Yang et al.PubMed showed that increase in $CD8^+$ cytotoxic T-lymphocytes in peripheral blood might serve as a source of IFNγ, which, as demonstrated by authors, directly affects melanogenesis and induces melanocyte apoptosis, thus providing another mechanism for melanocyte dysfunction and destruction in vitiligo.

Ding et al.PubMed showed that melanocytes in perilesional skin in case of vitiligo and halo nevi have different morphological alterations in mitochondria thus suggesting heterogeneous nature of these two conditions.

Eby et al.PubMed advanced a previous finding on the role of defective skin homing of regulatory T-cells in vitiligo, and showed that CCL22 can efficiently promote regulatory T-cell homing to skin to suppress vitiligo in two mouse models of vitiligo. These findings suggest that CCL22 can be used as a basis for vitiligo therapy development.

Wagner and coauthorsPubMed revealed that the cell adhesion molecule E-cadherin is lost or abnormally distributed on melanocytes in vitiligo patients long before clinical appearance of lesion. In addition, it has been shown that E-cadherin abnormalities sensitize melanocytes to detachment which leads to melanocyte death under oxidative or mechanical stress, known vitiligo triggers. These findings reveal melanocyte

adhesiveness as a potential target for therapeutic intervention and suggest existence of predisposition to vitiligo development. Notably, recent study of Tarle et al.PubMed (see below under *Genetic studies*) points on genetic variation in E-cadherin-encoding gene, *CDH1*, as a risk factor for vitiligo.

After examination of 45 patients with active vitiligo, Zhou et al.PubMed found an increased level of Th17 cells and Th17-related cytokines in circulation which correlated with increased body surface area involvement, thus adding another piece of evidence to involvement of Th17 cells in vitiligo pathogenesis.

Gong et al.PubMed investigated the effect of calcipotriol on hydrogen peroxide-challenged melanocytes in culture, with the data obtained pointing on the capacity of calcipotriol to reduce oxidative stress in melanocytes which is considered as one of the possible trigger of autoimmune response besides direct melanocyte destruction. However it should be noted that clinically relevant effects of vitamin D3 analogues remain a questionable issue.

Farhan et al.PubMed found that vitiligo patients with comorbid type I diabetes are characterized by elevated level of interleukin-6 compared to healthy individuals and vitiligo patients lacking this comorbid disease. However, these findings are to be considered as preliminary owing to limited sizes of studies cohorts, might point to differences in pathomechanisms of vitiligo and diversity of molecular basis of the disease.

Genetic studies

Badran et al.PubMed studied association of angiotensin converting enzyme gene (*ACE*) insertion/deletion polymorphism with vitiligo in a case-controlled study of 100 vitiligo patients and 100 healthy controls, with the finding of statistically significant association. In addition, significant difference in *ACE* gene genotype distribution was observed for segmental, nonsegmental and focal vitiligo thus indirectly supporting different molecular mechanisms of vitiligo pathogenesis in these clinically distinct forms. However, small study cohorts questions reliability of study results.

Li et al.PubMed conducted a meta-analysis of studies on association of vitamin D receptor (*VDR*) gene polymorphism with vitiligo. Authors concluded that this polymorphism might confer susceptibility to vitiligo in East Asian populations.

Jun et al.PubMed reported a major association of vitiligo with major histocompatibility class I gene allele HLA-A*02:01, with some differences from Caucasian population being observed.

Tarle et al.PubMed found that genetic variation in *CDH1* gene encoding E-cadherin adhesion molecule is associated with vitiligo, especially in the presence of autoimmune comorbidities, which is well in line with findings of Wagner et al.PubMed on the potential role of E-cadherin abnormalities in vitiligo pathogenesis.

Zayed et al.,PubMed in an assumption that promoter polymorphism in inducible nitric oxide synthase (*iNOS*) gene is associated with increased iNOS production and oxidative conditions contributing to melanocyte destruction, investigated effect of two *iNOS* promoter polymorphisms on susceptibility to vitiligo on a cohort of 100 vitiligo patients and 100 healthy indiduals' group. Based on results of the study, authors concluded that *iNOS* promoter variations might contribute to genetic susceptibility to vitiligo, although size of study cohorts does not allowing for a firm conclusion and warrant further large-scale studies.

Candidate biomarkers

As reported by Zhou et al.,PubMed (see *Understanding mechanisms of vitiligo pathogenesis* section), increased level of Th17 cells and Th17-related cytokines in circulation might be potential marker of disease activity (although likely only in a subset of vitiligo patients).

Mechanisms of treatments

Goldstein et al.PubMed showed that narrow-band ultraviolet B (NB-UVB) induces proliferation, migration and differentiation of melanocyte precursors in vitiligo skin arising from primary melanocyte germ in hair follicle bulge, thus making another step in understanding of molecular and cellular mechanism of NB-UVB curative effect in vitiligo.

Dr. Passeron commented on the results of afamelanotide application in vitiligo treatment, pointing on the only mechanistically relevant response on repigmentation rate but not on its induction, which also might cause unwanted enhancement of contrast between lesional and normal skin in light-colored skin individuals.PubMed In response to the comment, Lim and coauthors agreed with this point of view, and pointed on the study design, which included pre-treatment with NB-UVB aiming to stimulate melanoblast differentiation.PubMed

Methodological advancements

Gupta et al.PubMed published a work on hypodermic needle as a dermabrading device used for preparation of recipient site for skin grafting in vitiligo.

Adotama et al.PubMed pointed out that patient's satisfaction is rarely assessed as a vitiligo treatment outcome, and conducted a cross-sectional study aiming to determine patient's satisfaction with commonly used treatments of vitiligo.

Ebrahimi et al.PubMed suggested using motor-driven dental lab finishing carbide bur for preparation of recipient site for epidermal transplantation procedure, with results of a pilot trial showing the reliability and efficiency of the method which allows safely, simply and precisely remove only depigmented epidermis, even in complex-shaped lesions.

Gupta et al.PubMed described a new technique for preparation of noncultured epidermal cell suspension for transplantation in stable vitiligo. The technique is distinguished by cell separation and harvesting inside a suction blisters, with an advantage of being simple and inexpensive.

Novel treatment modalities

Li et al.PubMed reported the results of a pilot trial of fractional CO_2 laser combined with topical betamethasone and NB-UVB as compared to laser combined with NB-UVB alone. An experimental treatment showed better results, thus potentially offering novel efficient treatment option of vitiligo in hard-to-repigment locations.

Clinical studies and trials

Eleftheriadou et al.PubMed published results of the electronic Delphi consensus study aiming to identify key outcome measurements of clinical trials in vitiligo. Besides identified three essential domains (repigmentation, side effects, and maintenance repigmentation), four additional domains were recommended (cosmetic acceptability of results, QoL, stopping vitiligo activity and tolerability/burden of treatment). Importantly, high consensus has been reached among participants of the study comprising dermatologists and researchers interested in vitiligo, vitiligo patients, representatives of regulatory agencies and journal editors internationally.

Shrestha et al.PubMed compared efficiency of topical mometasone furoate combined with either placental extract or tacrolimus on a cohort of 100 vitiligo patients randomly assigned to two groups. Results of the study showed better efficiency of combination with tacrolimus in localized vitiligo treatment, and did not added evidences to yet questionable efficiency of placental extract in vitiligo treatment.

Isedeh et al.PubMed reported a suboptimal response in segmental vitiligo patients treated with melanocyte-keratinocyte transplantation in their retrospective study. Although study cohort was small (10 patients), this observation warrants further study to conclude on suitability of this procedure in segmental vitiligo treatment.

Tien Guan et al.PubMed compared home-based phototherapy and hospital excimer lamp treatment efficiencies on a cohort of 44 vitiligo patients, with apparently (but not statistically significant) better results achieved in home-based settings.

Jang et al.PubMed reported the results of open-label clinical study of systemic corticosteroids, eximer laser and topical tacrolimus for treatment of recently onset localized vitiligo patches, with observed good results, which are expected as numerous studies revealed better efficiency of various treatments upon shorter disease duration, and combination of different treatment modalities performing better than monotherapy.

Koh et al.PubMed conducted a study of phototherapy efficiency in Asian children, with conclusion on better response in patients with generalized versus segmental disease type, and good safety and efficiency profile of the intervention. The highest response rate has been reported for NB-UVB, followed by other phototherapy treatments.

Tan & SakkanyPubMed concluded on efficiency of monobenzylether of hydroquinone as an effective depigmentation treatment of vitiligo based on the retrospective analysis of 53 cases.

Mohamed et al.PubMed reported good efficiency of combined treatment by CO_2 laser combined with 5-fluorouracil in treatment of hard-to-treat acral vitiligo compared to either modality alone. This report is in line with previously reported efficacy of 5-fluorouracil combined with ablative treatments on resistant lesions.

Reviewed and prepared by:
Dr. Igor Korobko, PhD, DSci.
Chief Scientific Director, Vitiligo Research Foundation
info@vrfoundation.org
www.VRFoundation.org
1-855-966-3555
1, Penn Plaza #6205
New York, NY 10119 USA
Published online on August 24, 2014

About Journal Of Pigmentary Disorders

Journal of Pigmentary Disorders is a scientific journal includes a wide range of fields in its discipline to create a platform for the authors to make their contribution towards the journal and the editorial office promises a peer review process for the submitted manuscripts for the quality of publishing. Journal of Pigmentary Disorders is one of the best Open Access journals of Scholarly publishing.

Journal of Pigmentary Disorders is scholarly Open Access journal and aims to publish the most complete and reliable source of information on the discoveries and current developments in the mode of original articles, review articles, case reports, short communications, etc. in all areas of melanoma, hyperpigmentation which includes post inflammatory hyperpigmentation, melisma & hypopigmentation disorders includes albinism, vitiligo etc. and making them freely available through online without any restrictions or any other subscriptions to researchers worldwide.

Submit manuscript at http://www.editorialmanager.com/biomedicaljournals/ or send as an e-mail attachment to the Editorial Office at editor.jpd@omicsgroup.org or editor.jpd@omicsgroup.us