OVERVIEW OF VITILIGO RESEARCH

April – June 2015

Contents

- Janus kinase inhibitors, in particular, tofacitinib, emerge as a novel treatment modality for vitiligo.

- A novel molecular link between oxidative stress in vitiligo and promotion of immune cell-mediated melanocyte destruction has been suggested.

- Genetic variation might be useful to predict efficiency of narrow-band ultraviolet B treatment of vitiligo.

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 April 2015 till June 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 April 01, 2015 and June 30, 2015. Retrieved records were manually checked for a relevance to and significance for the field of vitiligo research. Forty six records were found to be relevant and of interest, and were included in this quarterly overview.

Reviews & Comments

Van Driessche & Silverberg[PubMed] presented a review of current management of pediatric vitiligo. Colucci and coauthors[PubMed] published a review focused on interplay between oxidative stress and autoimmunity in vitiligo, and possible contribution of thyroid autoimmunity to vitiligo onset and maintenance.

Picardo & Bastonini[PubMed] published a comment on the appeared online in January paper of Wang et al.[PubMed] which was focused on the role of E-cadherin in vitiligo development, with highlights of some clinically significant implications. Harris[PubMed] commented on the work of Yang et al.[PubMed] published in February, which introduced a novel mechanism by which interferon γ might be involved in vitiligo, highlighting recently emerging interefrone γ signaling as a possible druggable target in vitiligo. In turn, Antonelli et al.[PubMed] summarized recent understanding of interferon γ signaling involvement in vitiligo with the focus on its components, in particular CXCL10 chemokine, as druggable targets.

Kemp[PubMed] commented the paper of Tembhre et al.[PubMed] published online in 2014, in which it was found that patients with active vitiligo manifest regulatory T-cell abnormalities, which might affect their functions and homing, in particular, suggesting a role of PD1/PDL pathway played in regulatory T-cell abnormalities in active vitiligo.

Finally, Sun et al.[PubMed] reviewed recent advances in nano- and micro-particles designed for improved topical delivery of bioactive substances which might be helpful in development of novel or improving efficiencies of existing agents for vitiligo treatment.

Disease Management And Clinical Features

Sosa and co-authors[PubMed] concluded that confetti-like depigmentation might be considered as a negative prognostic factor in vitiligo patients, which correlates with rapid disease progression and disease severity.

Sarvesh and co-authors[PubMed] used polarized light dermoscopy to analyze evolving vitiligo lesions. Authors noted that this method might be useful to distinguish initially evolving vitiligo from normal skin.

Ohguchi et al.[PubMed] analyzed data on 713 Japanese vitiligo patients, and besides epidemiological features, reported efficiencies for three types of treatments (phototherapy, vitamin D3 and punch grafting) for generalized, localized and segmental vitiligo thus permitting selection of the most appropriate treatment modality for a particular vitiligo subtype.

Komen et al.[PubMed] reported development of self-assessment tool for patients to evaluate degree of depigmentation which is based on Vitiligo Area Scoring Index, and evaluated its reliability. Such a self-assessment tool might be useful in large-scale epidemiological studies as well as contribute to patient's perception of disease treatment. At the same time, Ukoha et al.[PubMed] pointed that self-reported questionnaires as a source of data on vitiligo assessment greatly rely on accuracy of the patient for diagnosis and assessment itself, so there is a need for validation of data collected using this approach.

Epidemiology

Mu et al.,[PubMed] based on a retrospective study of 208 children, concluded that early-onset (before age of 3 years) vitiligo is associated with more extensive and progressive course.

Oninla et al.[PubMed] reported hospital-based statistics of dermatological diseases among pediatric patients in Nigeria, with vitiligo encompassing 5.3% and being at the forth place.

Lee et al.[PubMed] reported hospital-based statistics of vitiligo for the whole Korean population, with the determined prevalence being 0.12%-0.13%.

Comorbidities

Abolhassani et al.[PubMed] studied 57 symptomatic patients with selective immunoglobuline A deficiency with the findings on increased rate of several autoimmune diseases including vitiligo.

Besides vitiligo prevalence, the hospital-based whole-Korean study of Lee et al.[PubMed] revealed increased incidence of thyroiditis, atopic dermatitis and psoriasis among vitiligo patients.

Quality of life (QoL)

Ezzerdine et al.[PubMed] reported results of their analysis of overall vitiligo burden in relation with skin phototype.

Vitiligo triggers

Silverberg & Silverberg[PubMed] in their study of 1541 adult vitiligo patients reconfirmed that psychological stressors should be considered as possible vitiligo triggers.

Namazi[PubMed] hypothesized that pre-existing lowered level of glucose-6-phosphate dehydrogenase frequently reported in vitiligo patients might bring susceptibility to environmentally induced vitiligo triggers which act through depletion of glucose-6-phosphate dehydrogenase with concomitant manifestation of oxidative stress, a known factor in vitiligo pathogenesis.

Case reports

Srivathsa[PubMed] reported a case of oral vitiligo successfully stopped by minipulse therapy, with the emphasis that dentists should pay attention to initial vitiligo in their practice to timely control spread of depigmentation. Jha et al.[PubMed] reported repigmentation onset after bimatoprost application for periorbital vitiligo after unsuccessful prolonged use of topical steroids and tacrolimus. This report supports reported previously potential use of prostaglandins in vitiligo treatment, yet in the reported case treatment was discontimued due to localized hypertrichosis as a side effect.

Understanding mechanisms of vitiligo pathogenesis

Immunohistochemical study on 20 patients with non-segmental vitiligo conducted by Elgarhy et al.[PubMed] confirmed reduced DDR1 expression in lesional skin thus further supporting previously suggested role of DDR1 in vitiligo pathogenesis through reducing melanocyte adhesion. Notably, earlier two studies reported association of *DDR1* genetic variants with vitiligo susceptibility.

Wang et al.[PubMed] presented a hypothesis of RNASET2 RNase role which genetic variation has been recently linked to vitiligo susceptivility, in vitiligo pathogenesis based on various experimental data, suggesting that RNASET2 which is overexpressed in vitiligous skin and in stressed melanocytes and kerationocytes in culture, might have dual role, one consisting from direct induction of cell death, and the other (which is a subject for further investigation) serving as an "alarm signal" for immune cells to induce autoimmunity. Li et al.[PubMed] presented data linking in a novel way oxidative stress and autoimmunity through induction of chemokines under oxidative stress conditions which support $CD8^+$ T-cell trafficking to skin and melanocyte destruction.

Nouri-Koupaee et al.[PubMed] assessed balance between Th1 and Th2 T-helper cell subsets in peripheral blood of vitiligo patients by comparing expression levels of transcripts specific for these cells. In a result of the study, authors found higher expression of Th1-specific transcripts and lower expression of Th2-specific transcripts in vitiligo patients compared to healthy controls thus suggesting the role of Th1/Th2 imbalance in vitiligo.

Guntas et al.[PubMed] reported elevated ferric-reducing antioxidant power and prooxidant-antioxidant balance in vitiligo patients, thus again re-confirming increased oxidative stress in vitiligo. Results of the study show that these parameters (especially prooxidant-antioxidant balance) might serve as a measure of oxidative stress in vitiligo patients with possible clinical utility.

Genetic studies

Liang et al.[PubMed] conducted meta-analysis of case-controlled studies which looked for association between *CTLA-4* (+49A/G) polymorphism with vitiligo susceptibility. In agreement with previous reports pointing on weak (if any) association which might be secondary to other co-morbid autoimmune diseases, authors concluded that *CTLA-4* (+49A/G) polymorphism may not contribute to vitiligo (as well as psoriasis) onset risk.

Dai et al.[PubMed] conducted an analysis aiming to link genetic variation in nucleotide excision repair system genes to efficiency of vitiligo phototherapy. Authors found that indeed presence of a specific variation in *ERCC1* genes confers better efficacy of narrow-band ultraviolet B treatment.

Li et al.[PubMed] after analysis of 552 Han Chinese vitiligo patients and 1656 healthy controls reported that variant of *rs2456973* polymorphism at 12q13.2 is associated with presence of vitiligo comorbid immune-related diseases (with fairly low odds ratio of 1.27) as well with early vitiligo onset.

Cui et al.[PubMed] found that polymorphism in *miR-196-2* microRNA affects risk of vitiligo (although study cohorts were relatively small, only 116 individuals each). In addition to this, low risk genetic variation correlated with low serum tyrosinase immunoreactivity in serum, and genotype accompanied by low serum tyrosinase immunoreactivity resulted in decreased tyrosinase expression in PIG1 cells with concomitantly decreased apoptosis rate and reactive oxygen species levels. These findings, although being preliminary, further support recently suggested role of microRNAs in vitiligo pathogenesis.

Candidate biomarkers

Atas et al.[PubMed] analyzed folate, homocysteine and vitamin B12 levels in vitiligo patients before and after narrow-band ultraviolet B phototherapy. Their findings on higher baseline level of homocysteine and lack of difference in folate and vitamin B12 in vitiligo patients (60 subjects) compared to healthy controls are compatible with previous reports. After treatment, only vitamin B12 level changed in vitiligo patients, and decrease in it has correlation (although moderate but statistically significant) with treatment efficiency. Authors emphasized that further studies are required to clarify influence of phototherapy on folate, homocysteine and vitamin B12 levels in serum as well as point out on the possible need to assess skin homocysteine level to elucidate effect of phototherapy.

Mechanisms of treatments

Goldstein et al.[PubMed] described an emerging technique based on taking whole-body 3D-imaging and its subsequent analysis to objectively quantify skin area affected by vitiligo, which will be a useful tool in assessing treatment efficiency at a standardized manner.

Moreira et al.[PubMed] investigated mechanism of action of popular Asian folk medicine entity, *Pyrostegia venusta* leaf extract, upon systemic and topical administration using two animal models. Results of the study showed that the preparation indeed showed anti-inflammatory and hyperpigmenting effects, thus providing a rational for its beneficial effects for vitiligo.

Methodological advancements

Kaliyadan & Kuruvilla[PubMed] reported on the possibility to use hand-held black-light compact source which are readily available from online stores instead of specialized

Wood's lamp, thus providing equally performing, compact and cheap alternative to Wood's lamp.

Novel treatment modalities

Craiglow & King[PubMed] reported a case of vitiligo patient who was successfully treated with Janus kinase inhibitor tofacitinib. This observation is well in line with recently suggested role of interferon γ signaling in vitiligo pathogenesis in which Janus kinases are involved.

Several papers appeared this quarter which are focused on low-dose sequential-kinetic-activated cytokines. In the *in vitro* study,[PubMed] low-dose interleukin-10, β-endorphin, interleukin-4 and basic fibroblast growth factor displayed positive effect on redox homeostasis and improved viability of perilesional kerationocytes. In another work, Lotti et al.[PubMed] showed that low-dose cytokine treatment resulted in substantial repigmentation in vitiligo patients, especially when combined with microphototherapy. Finally, Lotti and co-authors[PubMed] summarized current knowledge in the field of low-dose medicine and hypothesized on their potential use in different dermatological conditions including vitiligo.

AlGhamdi et al.[PubMed] reported results of *in vitro* study of different laser irradiation on melanocyte viability, proliferation and migration. Authors found that all tested lasers (457 nm, 635 nm and 355 nm) had stimulatory effects but only at low levels of energy density, with 457 nm laser showing better effect. These finding put the ground for future rational use of lasers in vitiligo treatment.

Clinical studies and trials

Komen et al.[PubMed] conducted small clinical trial of cell suspension transplantation for stable segmental vitiligo and piebaldism (5 patients each) using automated cell suspension preparation with ReCell device. Authors observed good repigmentation rate which correlated with number of transplanted viable melanocytes thus emphasizing involvement of transplanted melanocytes in repigmentation.

Soliman et al.[PubMed] compared treatment with excimer laser alone or in combination with topical antioxidants, with the conclusion on feasibility of adding topical antioxidants to excimer laser phototherapy to improve treatment efficiency. In turn, Bae and collegues[PubMed] reported results of retrospective study of excimer laser, topical tacrolimus and short-term systemic corticosteroids in segmental vitiligo treatment. Based on analysis of 159 cases, authors concluded that the combination is a useful therapeutic option for segmental vitiligo, with several prognostic factors (including disease duration which again emphasize the need for early-after-onset treatment of vitiligo) being identified.

Verma and co-authors[PubMed] conducted a small (27 patients) comparative study of cultured versus non-cultured melanocyte transplantation, with the results suggesting that along with potency to cover bigger areas with the same amount of starting material, transplantation of cultured melanocytes gave better results in terms of repigmentation compared to the use of non-cultured cell.

Gou et al.[PubMed] assessed efficiency and predicative factors of success for treatment of vitiligo with suction blister grafting. While being efficient in general, this technique showed the best results in younger patients, and highest pigment spread was observed for face and neck. The limitation of the study was relatively small (28) number of patients enrolled.

Hosseinkhani et al.[PubMed] compared cosmetic formulation with traditional Iranian sabgh formulation used to color the skin, as camouflage for vitiligo patients, with similar improvement in QoL as assessed by Dermatological Life Quality Index scoring. Thus this traditional Iranian formulation can serve as an alternative to cosmetic camouflage products designed for vitiligo.

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