OVERVIEW OF VITILIGO RESEARCH

October – December 2015

Contents

Highlights

- Blocking JAK1/2 activity with ruxolitinib might be a strategy in vitiligo treatment but future studies are required to confirm efficiency and safety.

- Mechanisms underlying improved efficiency of NB-UVB phototherapy for vitiligo when combined with topical tacrolimus are described.

- Once-a-week treatment with targeted UVB seems to as efficient as conventionally accepted twice weekly schedule (in terms of administered UVB dosage and number of sessions) in inducing repigmentation of vitiligo lesions.

- Additional excimer laser phototherapy combined with NB-UVB for lesions with slow response or no further improvement with NB-UVB treatment might improve overall repigmentation

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 October 2015 till December 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 October 01, 2015 and December 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

In the paper appeared in the Journal of American Academy of Dermatology, the Vitiligo Working Group emphasized again that vitiligo should not be considered as a cosmetic defect, but rather as a disease.PubMed

Whitton et al.PubMed published an update of 5 year-old Cochrane systematic review of interventions for vitiligo. Authors concluded that there are still important variations in study design and outcome measures. As revealed, in a short-term follow-up, topical corticosteroid and narrow-band ultraviolet B (NB-UVB) phototherapy in combination with topical preparations showed the best evidences, and long-term follow-up are needed.

Harris discussed evidences for cellular stress contribution to autoimmune pathogenesis through linkage with immune response.PubMed Also, Boniface et al.PubMed presented a review focused on understanding of immune system role in vitiligo pathogenesis with the emphasis on an emerging link between cellular stress, melanocyte function and immune system.

Zanardelli et al.PubMed discussed perspectives of melanocyte precursor cell application in vitiligo treatment, and Chua and co-authors discussed important impact of skin phototype on vitiligo phototherapy.PubMed

Phiske published a review focused on childhood vitiligo, including its epidemiology, comorbidities and treatment modalities.PubMed

Harris commented the recently published work of Regazzetti et al.,PubMed emphasizing the role of Wnt signaling in oxidative stress-induced vitiligo and Wnt signaling pathway agonists as a promising class of anti-vitiligo treatments.PubMed

RainaPubMed and KaushalPubMed commented previously published work of Sangma et al.,PubMed questioning the study design and methodology used.

Disease Management And Clinical Features

Cohen et al.PubMed reported that presence of halo nevus in pediatric vitiligo patients is associated with generalized type of the disease but does not affect risk of disease progression. van Geel and co-authors reported results of study aiming to evaluate disease cessation as a factor affecting treatment motivation.PubMed

Bohm presented an overview of differential diagnosis of hypomelanotic conditions,PubMed among which vitiligo is the most abundant one.

Epidemiology

Kayal et al.PubMed compared clinical features of adult versus childhood onset vitiligo in Rajastan patients, revealing differences in gender predominance and initial site of depigmentation.

Comorbidities

Gill and co-authors reported results of large-scale (more than 1000 US vitiligo patients) cross-sectional study of co-morbid autoimmune diseases.PubMed Among 20% of patients

having at least one co-morbidity, higher prevalence compared to the reported for the US population was revealed for thyroid disease, alopecia areata, inflammatory bowel disease, pernicious anemia, systemic lupus erythematosus and some other autoimmune conditions. This report again confirmed higher prevalence of autoimmune co-morbidities in vitiligo patients and revealed some new associations.

In a pilot study, Khurrum et al.PubMed questioned about relationship between glaucoma or cataract prevalence, periorbital steroid use and vitiligo, with no evidence of their interconnection preliminary revealed.

Quality of life (QoL)

Study of Bonotis and co-authorsPubMed revealed that impact of vitiligo on QoL is significantly associated not only with disease variables but also is strongly affected by subjective factors.

Salzer et al.PubMed developed another toll (the Vitiligo Impact Scale, VIPs) to assess vitiligo burden in vitiligo patients consisting from 29 items with some question selectivity depending on a skin type, and carried out its validation.

Vitiligo triggers

Jung et al.PubMed reported a case of vitiligo development in a patient treated with adalimumab, a tumor necrosis factor-α (TNFα) blocker, thus adding experimental evidences on previously witnessed capacity of this type of pharmaceuticals to trigger vitiligo.

Choudhary reported a rare case of vitiligo onset in a naïve patient after initiation of radiotherapy.PubMed

Case reports

De CarvalhoPubMed reported a case of association of vitiligo with rheumatoid arthritis, an autoimmune disease with shared to some degree genetic susceptibility factors. In turn, Veitch and co-authorsPubMed describe rare co-localization of vitiligo and lichen planus. Adding to this, Langly et al.PubMed reported a rare case of co-morbid and co-localized vitiligo and psoriasis.

Mercier et al.PubMed reported a case of vitiligo after photodermatitis development in HIV patient.

Tang et al.PubMed reported successful repigmentation of vitiligo lesions in a result of epidermal cell suspension transplantation in a patient after bone-marrow transplantation, thus pointing on suitability of the method used for treatment in patients underwent bone marrow transplantation.

Understanding mechanisms of vitiligo pathogenesis

Zhu et al.PubMed in their study of anti-melanocyte autoantibody repertoire in vitiligo patients observed correlation between high anti-TRP-1 antibody and HSP70 levels, which indirectly support previously suggested role of HSP70 protein in triggering immune response against melanocytes.PubMed In addition, authors revealed correlation between hepatitis virus B (HBV) infection and vitiligo, thus pointing on possible role of viral infection in vitiligo onset, although this data are to be considered with caution as only 4 HBV infected patients were enrolled.

Results of Hua et al.PubMed showed that vitiligo onset could be associated with clinical benefit for melanoma patients treated with pembrolizumab which acts against immune system response controlling receptor. This observation adds additional evidence to autoimmune nature of vitiligo. Similarly, vitiligo was recorded as factor associated with improved overall survival of melanoma patients treated with nivolumab, another immunotherapeutic agent with similar mechanism of action.PubMed

Lim et al.PubMed analyzed prevalence of elevated autoantibody levels in vitiligo patients, with a conclusion that anti-thyroid and anti-nuclear antibody levels are equally present in both segmental and non-segmental vitiligo patients, thus assuming contribution of autoimmune component to segmental vitiligo pathogenesis.

Nagui et al.PubMed reported correlated levels of proopiomelanocortin (POMC) and melanocortin 1 receptor (MC1R) transcripts in both normal and lesional vitiligo skin, and their decrease in vitiligo lesions, thus suggesting possible role of melanocortin system in vitiligo pathogenesis.

Dey-Rao & Sinha reported results of pathway and interactome computer analysis hinting on novel key transcriptional regulators involved in vitiligo pathogenesis.PubMed

Genetic studies

Lee & BaePubMed concluded from meta-analysis that polymorphism in interferon-γ (IFNγ)-encoding gene promoter (nt 874) is not associated with vitiligo despite being previously linked to some other autoimmune diseases. Nie et al.PubMed presented results of meta-analysis of linkage for TNFα gene 308G/A polymorphism with vitiligo susceptibility, with the conclusion suggesting the lack of association (which is also confirmed by the results of several genome-wide association studies). Yu et al.PubMed found association of melanocortin receptor 1 polymorphism with vitiligo susceptibility in Taiwanese population in a case-controlled study, which is in line with previously revealed association in genome-wide association study.PubMed

Traks et al.PubMed in a case-controlled study revealed association of innate immune system receptor gene, *TLR7*, with vitiligo, however number of subjects (139 vitiligo patients and 307 healthy controls) is too low to make definite conclusion. Similar drawback can be assigned to another work suggesting linkage of familial vitiligo with genetic variation near the gene encoding interleukin-26, and female vitiligo with variation in *IFNAR1* gene.PubMed

Candidate biomarkers

Anbar et al.PubMed attempted to solve an existing contradiction whether homocysteine level is increased in vitiligo patients. While found no difference in serum homocysteine level, authors observed increase in homocysteine in induced blister fluids, thus suggesting presence of local events occurring in active vitiligo lesions. Osman et al.PubMed analyzed levels of interleukin (IL)-17, IL-23 and transforming growth factor β (TGFβ) in vitiligo patients, with the finding on decreased TGFβ serum level in vitiligo patients, which is in line with some previous studies and hints on recently emerging role of regulatory T-cells in vitiligo pathogenesis.

Abreu et al.PubMed presented literature review aiming to identify immunological factors associated with vitiligo treatment outcome. Authors point on skin-infiltrating cytotoxic CD8+ T-cells as major cellular predictors of treatment success as well as on other parameters such as cytokines and regulatory T-cells as potential biomarkers.

While occurrence of individual cytokine level variations in vitiligo patients is a contradictory issue owing to opposite results frequently presented by different research groups, the study of Ala et al.PubMed suggests that ratio of IFNγ level to that of interleukin-10 (but individual cytokine levels) is typically altered in vitiligo patients and correlates with some clinical and anamnestic features.

Doss et al.PubMed revealed that vitiligo patients in the studies cohort (n=30) are characterized by lowered serum vitamin D level and skin vitamin D receptor expression, although in a view of previous study results, vitamin D insufficiency in vitiligo remains a contradictory issue and might hallmark a subgroup of patients. Indeed, Khurrum & AlGhamdiPubMed reported no difference in serum vitamin D level between vitiligo patients and healthy controls based on analysis of 300 subjects, with the observed correlations possibly being attributed to younger age, recent vitiligo onset, male gender and non-use of phototherapy. At the same time, Takci and co-authors reported universal lack of plasma 25-hydroxyvitamin D in Turkish vitiligo patients after studying 44 vitiligo patients and 43 healthy subjects.PubMed

Zhu et al.PubMed studied anti-melanocyte autoantibody repertoire in vitiligo patients and identified novel melanocyte membrane vitiligo-associated antigens.

Wu et al.PubMed reported results of pilot (10 patients involved) study suggesting that granulocyte-macrophage colony stimulating factor (GM-CSF) serum level might serve as a biomarker useful in prediction of cultured melanocyte transplantation outcome in vitiligo treatment. Authors suggest that increased (compared to non-responders) GM-CSF level can contribute to melanocyte proliferation and melanogenesis after transplantation.

Mechanisms of treatments

Jung et al.PubMed showed that tacrolimus, a widely used topical agent in vitiligo treatment, promotes melanosome maturation and stabilize tyrosinase as well as enhance UVB-induced their transfer from melanocytes to keratinocytes. These findings reveal novel regulatory mechanism underlying and explaining improved efficiency of NB-UVB in combination with tacrolimus in vitiligo treatment.

Methodological advancements

Matsuzaki et al.PubMed discussed specialities of application of cultured epithelial sheet grafting for male genital vitiligo treatment. Gupta et al.PubMed suggested minimally invasive and scarless technique for donor skin collection for epithelial cell suspension transplantation for vitiligo treatment.

Despite being "a golden standard" in vitiligo treatment, Madigan et al.PubMed pointed on a lack of unified evidence-based guideline for NB-UVB phototherapy for vitiligo, and suggested to stimulate discussion aiming to develop with unified protocol.

Novel treatment modalities

Harris et al.PubMed reported a case of vitiligo repigmentation as a side effect of ruxolitinib (inhibitor of JAK1 and JAK2 protein kinases activated in response to cytokine and growth factor actions on cell) administration. This observation might hint on a novel strategy in vitiligo treatment.

Wang et al.PubMed reported rare case of vitiligo resolution after excision of halo congenital melanocytic nevus, suggesting permissive environment in the latter for triggering and maintaining vitiligo and a novel approach in vitiligo treatment in such patients.

Based on reactive oxygen scavenger properties of ethyl vanillate, Namazi & Shotorbani evaluated its topical preparation as adjuvant to NB-UVB phototherapy topical treatment. Topical ethyl vanillate potentiated NB-UVB-induced repigmentation of vitiligo lesions, although the observed effect was clinically mild.PubMed

Clinical studies and trials

Ibrahim et al.PubMed studied effect of intradermal platelet-reach plasma injection on efficiency of NB-UVB phototherapy of vitiligo, with the conclusion on increased efficiency of the treatment through shortening duration of phototherapy and increasing patient's compliance.

Lopes and co-authors reported results of systematic review and meta-analysis of efficacy and safety 308 nm excimer lamp phototherapy for vitiligo in comparison with other types of phototherapy.PubMed Authors concluded on similar efficiency and safety profile of excimer lamp, excimer laser and conventional 311 nm NB-UVB.

Kim et al.PubMed demonstrated that leukotrichia is a negative prognostic factor in both segmental and non-segmental vitiligo patients receiving excimer laser therapy, thus further confirming that presence of leukotrichia is a sign of a poor prognosis in vitiligo treatment, most likely owing to exhausted hair follicle melanocyte reservoir.

Meta-analysis of published results of clinical trials showed that calcineurin inhibitors are superior over placebo as a monotherapy in treatment of vitiligo, as well as improves of phototherapy results when used in combination. However, combination of calcineurin inhibitors with phototherapy is still a poor option to treat vitiligo lesions in UV-resistant sites.PubMed Bagherani reported results of a new comparative study of pimecrolimus versus clobetasol propionate in a treatment of localized vitiligo.PubMed

Shin and co-authors applied excimer laser treatment on lesions slowly or not responding to NB-UVB phototherapy while continuing NB-UVB sessions, with further improvement observed in more than a half of patients.PubMed Thus, this approach might further increase repigmentation without remarkable side-effects, although the method showed poor efficiency in repigmentation of lesions with commonly resistant to treatment acral localization.

Lee et al.PubMed reported high efficiency of combination of oral mini-pulse steroids and NB-UVB in stopping vitiligo progression (in 100% out of 32 patients involved) and subsequent repigmentation. However, no control group was included, so contribution of individual treatments or their synergistic effect remains unclear.

Majid and Imran reported results of the study aiming to compare once- versus twice-weekly targeted UVB treatment regimes, with unexpected conclusion on similar efficiency of repigmentation in terms of administered UVB dosage and number of sessions.PubMed

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Published online on April 30, 2016