OVERVIEW OF VITILIGO RESEARCH

July – September 2015

Contents

- The Vitiligo Noticability Scale, a novel tool to measure vitiligo treatment efficiency, beats routinely used percentage of depigmented skin in reflecting both patient- and clinician-reported global treatment success.

- Genetic variation might predict efficiency of phototherapy for vitiligo

- Wnt signaling pathway and *miR-25* microRNA emerge as novel possible targets in vitiligo treatment

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 July 2015 till September 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 July 01, 2015 and September 30, 2015. Retrieved records were manually checked for a relevance to and significance for the field of vitiligo research. Fifty three records were found to be relevant and of interest, and were included in this quarterly overview.

Reviews & Comments

Xie et al.PubMed summarized current knowledge on interplay between oxidative stress and triggering autoimmune reaction as a driver of vitiligo. KempPubMed overviewed experience and perspectives of tumor necrosis factor-α antagonist use in vitiligo treatment, with review of Webb et al.PubMed on the same topic suggesting that tumor necrosis factor-α blockers might be beneficial for patients with actively spreading vitiligo although a risk of vitiligo initiation is a concern. Lotti et al.PubMed published a review focused on a novel paradigm in vitiligo treatment, the activated low-dose cytokine therapy, which has been also highlighted by Rivkina et al.PubMed Sokolova et al.PubMed in their review summarized data on safety and efficiency of narrow-band ultraviolet B (NB-UVB) phototherapy in dermatology including application for vitiligo treatment. Cohen et al.PubMed presented a review of alternative treatments for vitiligo, and Jahan with co-authorsPubMed published a review focused on the role of *FOXP3* gene variations in defining vitiligo susceptibility.

Disease Management And Clinical Features

Batchelor et al.PubMed evaluated a novel patient-reported vitiligo treatment outcome measurement tool, the Vitiligo Noticability Scale (VNS). In this pilot study, authors found significant correlation of VNS with both patient- and clinician-reported global treatment success. Importantly, routinely used percentage of repigmentation showed weaker association. Thus VNS emerges as a better and more consistent indicator of treatment success, which should be further validated in large-scale studies.

Epidemiology

Based on analysis of 100 Indian male patients with nonvenereal genital dermatoses, Saraswat et al.PubMed identified vitiligo as the most frequently encountered one (18%) among 15 others conditions presented.

Comorbidities

Hammoud et al.PubMed conducted a meta-analysis of studies aiming to assess a risk of melanoma and non-melanoma skin cancer in vitiligo patients. Authors' results confirmed that vitiligo patients have lower risk of skin cancer development, with possible reasons for this phenomenon being discussed.

Saylam Kurtipek et al.PubMed after analysis of 108 Turkish vitiligo patients found lower that previously reported rate of thyroid dysfunction, thus arguing the need for routine examination of vitiligo patients (at least in Turkish population) without clinical history for thyroid abnormalities. On the contrary, Yazdanpanah et al.PubMed confirmed high prevalence of thyroid disease in a group of Iranian vitiligo patients, with no difference found for patients with active or stable disease.

Results of Karadag et al.PubMed obtained for 61 vitiligo patients, suggest eye involvement, with vitiligo patients possibly being more prone to dry eye syndrome,

although larger studies are needed to confirm this. In line with this, Dogam et al.PubMed indeed reported apparent association between vitiligo and dry eye syndrome.

Quality of life (QoL)

EleftheriadouPubMed developed a novel vitiligo burden questionnaire, which might facilitate development of consensus vitiligo treatment outcome measurement.

Boza et al.PubMed conducted translation, cross-cultural adaptation and validation of vitiligo-specific health-related QoL questionnaire (VitiQol) into Brazilian Portuguese thus enabling conduction of QoL studies among Brazilian vitiligo patients using this specific evaluation tool.

Vitiligo triggers

Wu et al.PubMed analyzed permanent hair dyes as vitiligo trigger.

Case reports

AlJasser et al.PubMed analysed series of cases comprising from 127 vitiligo patients treated by NB-UVB, for photolichenoid papule complications. This type of complication has been observed with the frequency 3.1%, it was reversible upon phototherapy withdrawal and was associated with longer treatment duration and higher cumulative dose. Based on this observation, authors warrant prompt recognition and management of this complication of phototherapy in vitiligo patients.

Byun et al.PubMed reported a case of successful childhood vitiligo treatment by He-Ne laser and topical tacrolimus, supporting efficiency of this type of vitiligo treatment reported earlier.

Gaurkar et al.PubMed reported a unique case of sequential development of several autoimmune disorders including vitiligo in HIV-seropositive patient.

Zhou et al.PubMed reported the first case of discoid lupus erythematosus complicated with vitiligo and hyperthyroidism.

Understanding mechanisms of vitiligo pathogenesis

Wang et alPubMed investigated biological effect of protective genetic variant of aryl hydrocarbon receptor (*AHR*) gene variant and found that it confers increased transcriptional activity which correlates with increased production of regulatory T-cell cytokines, thus further extending knowledge about possible molecular pathomechanisms of vitiligo and providing a mechanistical link between genetic susceptibility to vitiligo and its impact on cellular and molecular processes.

Findings of Adly et al.PubMed on lowered glia-derived neurotrophic factor (GDNF) expression by vitiligo lesional keratinocytes suggest possible role of GDNF in vitiligo pathogenesis and prompt future studies in this direction.

Regazzetti et al.PubMed found that Wnt signaling pathway has specific alterations in vitiligo skin, namely, oxidative stress results in its down-regulation in both melanocytes and

keratinocytes, and Wnt signaling agonist induced repigmentation in depigmented vitiligo skin *ex vivo*. In summary, these findings point on Wnt agonists as a novel class of compounds potentially useful for vitiligo treatment.

Shi et al.PubMed found that oxidative stress results in induction of *miR-25* microRNA in both keratinocytes and melanocytes which is responsible, besides direct promotion of oxidative stress-driven melanocyte destruction, for lowered production of key melanogenic factors, SCF and bFGF, by keratinocytes. These findings enlighten *miR-25* microRNA as a potential target in vitiligo.

Wang et al.PubMed investigated possible role of Rnaset2 protein in vitiligo pathogenesis following previously identified genetic link between *RNASET2* and vitiligo. The authors found that stress conditions induce Rnaset2 production by melanocytes and keratinocytes with suppressive effect on melanocyte outgrowth and migration, thus providing possible link from genetic susceptibility to pathomechanism of vitiligo. Involvement of *RNASET2* gene in vitiligo might also be realized through the role of the Rnaset2 in regulation of antioxidant tone and response to oxidative stress as demonstrated by Caputa et al.PubMed

Machado do Nascimento et al.,PubMed based on genetic and biochemical evidences, suggested that *BCHE* gene and its expression product, butyrylcholinesterase, are involved in vitiligo pathogenesis.

Al-Shobaili & RasheedPubMed presented results of their study showing that oxidation of tyrosinase by reactive oxygen species might stimulate development of autoimmune reaction in vitiligo, thus providing yet another mechanism of melanocytic auto-antigen formation in vitiligo and additional role of oxidative stress as vitiligo trigger.

Genetic studies

KempPubMed reported association of *ERCC1* gene single-nucleotide polymorphism with NB-UVB phototherapy efficiency in vitiligo patients.

Results of case-controlled (281 cases) study of Schunter et al.PubMed suggest association of *FoxD3* transcription factor gene polymorphism with vitiligo and with thyroid immunoregulation as judged by association with elevated anti-Tg and anti-TPO antibody presence.

Results of meta-analysis conducted by Wu and co-authors suggest that -308 nt G/A polymorphism of tumor necrosis factor-α gene is not linked to vitiligo.PubMed At the same time, Lee & BaePubMed concluded that it might be a risk factor in Middle Eastern population.

Rashed et al.PubMed reported association of *ACE* gene insertion/deletion polymorphism with vitiligo based on analysis of small (74 and 75 subjects) comparison groups, which replicates previous results obtained for Egypt vitiligo patients.PubMed In addition, an association has been observed with higher VIDA score and interleukin-6 level. The discrepancy between several other reports on the lack of *ACE* polymorphism association with vitiligo might be reasoned by ethnic divergence of genetic susceptibility to vitiligo, while effects of small sizes of study cohorts and case-controlled study design cannot be excluded.

Candidate biomarkers

Edgunlu et al.PubMed assessed serum level of TNF-related apoptosis-inducing ligand (TRIAL) and its receptor DR4 gene polymorphism in vitiligo patients. While no genetic association has been revealed, vitiligo patients had higher level of TRIAL. However the elevation was minor, and its significance in vitiligo pathogenesis remains unclear.

Abdellatif et al.PubMed investigated serum level of GM-CSF in vitiligo patients and healthy controls (40 subjects in each group) and found that vitiligo patients have 2-fold higher GM-CSF level. This finding is in line with previous report of Tu et al.PubMed and further suggest that GM-CSF might be one of the determinants in autoimmune pathogenesis of vitiligo.

Along with possible role in vitiligo pathogenesis, Shi et al.PubMed observed correlation between microRNA *miR-25* serum level and disease activitiy.

Mechanisms of treatments

Ning et al.PubMed demonstrated that epigallocatechin-3-gallate (EGCG), a major constituent of green tee with potent anti-oxidant and anti-inflammatory activities, inhibit interferon-γ-induced activation of JAK2 protein kinase, a recently emerged promising target in vitiligo.

Lu et al.PubMed found that bilobalide, a main terpenoid constitutive of *Ginkgo biloba* extract, which was previously reported to be useful in vitiligo management, can attenuate hydrogen peroxide-induced melanocyte death, induce intrinsic cellular anti-oxidant defense system and reduce Hsp70 release, thus potentially (based on previously uncovered role of Hsp70 in vitiligo pathogenesis) suppressing autoimmune response against melanocytes.

Methodological advancements

Results of Gupta & DevendraPubMed demonstrated that microskin grafting is simple and efficient technique to treat genital vitiligo.

Sheth et al.PubMed reported development and initial validation of an automated computer-based image analysis program to objectively determine depigmentation area within a lesion. Development of software of this type would improve evaluation of treatment outcome, especially during clinical trials.

Novel treatment modalities

Garg et al.PubMed reported a development of novel ethosome-based hydrogel for improved skin delivery of methoxsalen. The developed delivery vehicle was characterized by enhanced percutaneous penetration of the drug with lowered phototoxicity and erythema observed in preclinical model.

Clinical studies and trials

Silpa-Archa et al.PubMed compared different methods of recipient site preparation and dressing compositions in melanocyte-keratinocyte transplantation. Authors concluded that broadly used dermabrasion is time- and labor-consuming while laser-assisted dermabrision, besides being costly, might increase risk of depigmentation. This experimental study was topped by a review on the topic by Al-Haldidi and co-authors.PubMed

Abdel Latif & IbrahimPubMed reported results of a left-right comparative study of 308 nm eximer light versus combination of topical steroids and vitamin D3 analogues on a group of 44 patients with localized and stable non-segmental vitiligo. Authors concluded that while the former treatment modality resulted in earlier onset of repigmentation, both treatments were efficient with no statistically significant difference at the end-point.

Park et al.PubMed unexpectedly found that combination of excimer laser phototherapy with topical tacrolimus, while being superior over either of the monotherapy at the beginning, likely does not provide better final (after 6 months) outcome than monotherapy.

Ashique & KaliyadanPubMed presented results of retrospective analysis of 30 stable vitiligo patients who underwent suction blister epidermal grafting, with the conclusion on better efficiency on lips and face compared to proximities, and on small compared to large patches. Authors observed high efficiency of the method, with 50% rate of excellent response.

BagheraniPubMed reported results of 308 nm excimer light phototherapy alone or in combination with topical khellin and/or tacrolimus in vitiligo treatment.

Singh et al.PubMed reported results of comparative studies of oral minipulse corticosteroid and low-dose methotrexate in active vitiligo treatment and found equal efficiency of these two treatments in ceasing vitiligo progression, thus offering an alternative treatment for patients with contradictions for corticosteroid use.

Bao et al.PubMed in a single-lesion comparative study found that blister roof grafting, cultured melanocyte and non-cultured cell suspension transplantations are equally efficient in vitiligo treatment, with blister roof grafting giving faster repigmentation onset followed by cultured melanocyte and non-cultured cell suspension transplantation.

Leone & Paro VidolinPubMed compared efficiency of excimer laser phototherapy combined with topical antioxidant cream or placebo in a left-right comparative study, with the finding on earlier repigmentation onset when antioxidant cream was used. However study cohort consisted from only 10 patients so the results should be considered as preliminary.

In line with several previous reports, Vachiramon and co-authorsPubMed reported that addition of laser-assisted skin ablation to combination of NB-UVB and topical steroids in some cases might improve efficiency of treatment of resistant vitiligo lesions.

Singh & NasirPubMed revealed that reservoir effect of clobetasol propionate and fluticasone propionate after their application on depigmented skin lasts for 5 days, so based on this data, reduction of frequency of topical steroid application for vitiligo treatment cab be considered.

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