OVERVIEW OF VITILIGO RESEARCH

October- December 2014

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- Topical latanoprost (prostaglandin F2α analogue) can be used (alone or in combination with NB-UVB phototherapy) to induce repigmentation of vitiligo lesions

- Infrequent topical tacrolimus can be used as prophylactics to prevent relapse after successful repigmentation

- Based on results of study in mice, simvastatin emerges as a novel treatment for vitiligo, capable to prevent vitiligo onset and to reverse already manifested disease

- Ethnical difference in vitiligo prevalence and associated comorbidities profiles has been further confirmed

- Level of reactive oxygen species in erythrocytes emerges as an indicator of vitiligo activity

- Involvement of regulatory T-cell abnormalities in vitiligo pathogenesis is gaining more support

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 2014 till December 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 October 01, 2014 and December 31, 2014. Retrieved records were manually checked for a relevance to and significance for the field of vitiligo research. Fifty one records were found to be relevant and of interest, and were included into this quarterly overview.

Reviews & Comments

Speeckaert et al.PubMed reviewed mechanisms of vitiligo pathogenesis with their link to success or failure of different treatments. In turn, Daniel & WittalPubMed published a treatment update for vitiligo. Shenoi & PrabhuPubMed presented a review on PUVA (psoralen plus ultraviolet A) therapy in vitiligo and psoriasis treatment, with a note that efficiency of NB-UVB (narrow-band ultraviolet B) is equal to or even better than that of PUVA but with fewer side effects.

Disease Management And Clinical Features

Feily suggested a new tool (VETI, vitiligo extent tensity tool) to assess vitiligo patients and treatment efficiency.PubMed

Sheth et al.PubMed analyzed the efficiency and precision of patient-administered Vitiligo Screening Tool (VISTO) designed to detect vitiligo in adult English-speaking population. As a result of the study authors concluded that VISTO is a simple, cost-effective and sensitive and specific self-administered tool to confirm vitiligo.

Komen and coauthorsPubMed presented results of a study aiming to evaluate reliability and responsiveness of VASI and VETF instruments used to measure vitiligo burden. Authors concluded that both instruments are reliable for assessment, yet care should be taken when using them due to relatively large smallest detectable changes.

Epidemiology

Kumar et al.PubMed reported results of hospital-based study of vitiligo prevalence in India. Vitiligo accounted for 9.98% of all dermatological cases, with 65.21% being patients with stable disease, the most frequent involvement of lower lip in mucosal vitiligo and lower limbs being the most frequent site of vitiligo onset.

Comorbidities

Chung et al.PubMed analyzed association of lichen planus with autoimmune comorbid diseases in a nation-wide study of Taiwanese patients. While association with several autoimmune diseases was revealed, no association between lichen planus and vitiligo has been observed. In a similar study of vitiligo patients, Chen et al.PubMed revealed much lower prevalence of vitiligo among Taiwanese (0.064%), later disease onset and different associated comorbidity profile compared to those reported for western population, which confirms results of similar large-scale studies previously conducted in China. Arunachalam and co-authorsPubMed presented results of study of prevalence of autoimmune thyroid disease in Italian patients with non-segmental vitiligo. Gopal et al.PubMed analyzed prevalence of autoimmune thyroid dysfunction and diabetes mellitus in Indian vitiligo patients (n=150) and healthy controls (n=100), and revealed increased prevalence of both diseases (20% vs 2% and 16% vs 5%, respectively). Finally, Mohan & SilverbergPubMed based on conducted systematic review and meta-analysis concluded that presence of vitiligo, especially early-onset one, significantly increases risk for

development of atopic dermatitis.

Quality of life (QoL)

Ignorvo et al.PubMed published their results on QoL estimation among Italian vitiligo patients using Dermatology Life Quality Index (DLQI) instrument for assessment in 9 dermatological centers, with the conclusion on limited impairment of QoL in Italian vitiligo patients compared to other reports, with expected correlations with female gender, stability of the disease over time and face involvement at disease onset having been observed. Study of Kruger and SchallreuterPubMed expectedly confirmed increased stigmatization, social anxiety/avoidance and psychological stress in vitiligo patients.

Vitiligo triggers

Van Geel et al.PubMed after analysis of a large cohort of subjects came to conclusion that congenital melanocytic naevi may influence the age of vitiligo onset and trigger development of halo naevi in patients with vitiligo.

Case reports

Zhang et al.PubMed reported a case of blue vitiligo development after intralesional injections of psoralens combined with UVB phototherapy (PUVB). This is the forth report supporting contribution of PUVB to development of blue vitiligo.

Yadav et al.PubMed reported a case of segmental vitiligo combined with segmental morphea and family history of autoimmune diseases. Authors suggest autoimmune link to explain co-occurrence and the role of existing cutaneous mosaicism in segmental appearance.

Walker and colleaguesPubMed reported a case of co-localized alopecia areata and vitiligo, interpreting this case as supporting a theory on common mechanisms of pathogenesis of these two autoimmune disorders.

Understanding mechanisms of vitiligo pathogenesis

Yanik et al.PubMed questioned whether psychiatric biomarker, serum level of brain-derived neurotrophic factor (BDNF), is altered in vitiligo patients. In their preliminary study (57 cases and 58 controls) they found that serum BDNF level is significantly lower in vitiligo patients, which might be linked to repeatedly reported association of vitiligo with psychiatric disorders.

Horna-Terron et al.PubMed presented a review on thioredoxin domain-containing protein 5 (TXNDC5), a chaperon molecule residing in endoplasmic reticulum, which provides a mechanistical ground for possible involvement of TXNDC5 in vitiligo previously suggested by genetic association study of Jeong and colleagues.PubMed

Maeda and colleaguesPubMed showed that regulatory T-cells can render self-reactive human cytotoxic CD8+ T-cells anergic thus precluding from autoimmune reaction. Importantly, authors demonstrated presence of such anergic T-

cells reacting against vitiligo antigens in skin of healthy individuals, thus further confirming critical role of regulatory T-cells in vitiligo pathogenesis. In turn, Tembhre et al.PubMed showed that patients with active vitiligo manifest regulatory T-cell abnormalities, which might affect their functions and homing, in particular, suggesting role of PD1/PDL pathway in regulatory T-cell abnormalities in active vitiligo. Further on, Lin et al.PubMed investigated the potency of regulatory T-cells from patients with active vitiligo to suppress activity of cytotoxic T-lymphocytes and found that this activity of regulatory T-cells is compromised in patients with progressing vitiligo compared with those with stable disease. The compromised inhibitory effect of regulatory T-cells was associated with reduced TGFβ production, which is in line with previous reports. In line with growing evidence of regulatory T-cell involvement in vitiligo pathogenesis, Dwivedi et al.PubMed presented a review on this topic.

Wang et al.PubMed reported differential microRNA profile in peripheral blood mononuclear cells of patients with non-segmental vitiligo, which might be linked to existing immune imbalance in vitiligo and further confirms previously pinpointed potential role of microRNAs in vitiligo pathogenesis.

Vaccaro et al.PubMed evaluated level of IL-23 on a small (18 patients) cohort of vitiligo patients. They found that vitiligo patients have increased serum IL-23 level, which also correlated with disease duration and activity, and extent of vitiligo. This observation although made on a small cohort, is in line with suspected role of Th17 cells in vitiligo and recent report of Zhang et al.,PubMed in which successful vitiligo treatment correlated with lowering of serum IL-23 level and lesional IL-23 expression.

Tsiskarishvili et al.PubMed attempted to correlate cytokine profile in vitiligo patients (IL-2 and IL-6) with presence of stress as vitiligo trigger in anamnesis. Unexpectedly, IL-2 and IL-6 levels were up compared to healthy controls if no stress preceded vitiligo onset but inverse relation was observed in patients with stress-induced vitiligo. These data, although require confirmation in a large-scale study, might hint at different mechanism of pathogenesis of stress-induced vitiligo, with the probable need for treatment adjustment.

Wang et al.PubMed showed that analogue of viral DNA can trigger melanocyte death and, more importantly, to stimulate pro-inflammatory cytokine production thus facilitating autoimmune response against melanocytes. These findings hint at possible contribution of viruses to vitiligo onset.

Results of Harris et al.PubMed showing potency of simvastatin to reverse and prevent vitiligo in an experimental mouse model along with revealed decreased production of interferon γ by melanocyte-specific $CD8^+$ T-cells further confirm suggested earlier role of interferon γ in vitiligo pathogenesis.

Genetic studies

Elhawary et al.PubMed assessed association of variations in TAP1 transporter and PSMB9 immunoproteasome component genes in a case-controlled study on 172 Saudi subjects. Authors found significant correlation between specific variants of these genes with the risk of vitiligo, although the drawback of the study is its case-controlled design and small study cohort.

Chang et al.PubMed in their genome-wide association study (GWAS) of X-chromosome aiming to find genetic associations with autoimmune diseases replicated previously identified in GWAS *FOXP3* association with vitiligo.

Aydingoz et al.PubMed found that concomitant presence of genetic variations in promoters of genes encoding TNFα and IL-10 is a risk factor for vitiligo, with respective cytokine level alterations seen in subjects, yet the sizes of study cohorts (n=105 for vitiligo and n=211 for controls) seems to be low to make a firm conclusion.

Candidate biomarkers

Pradhan et al.PubMed assayed if level of reactive oxygen species (ROS) in erythrocytes can be used to trace vitiligo activity. Their preliminary results obtained on cohorts of 21 vitiligo patients and 21 healthy volunteers showed that ROS level is higher in vitiligo patients, especially in those with active disease. If confirmed and stratified in larger studies, this parameter can be used as an objective measure of vitiligo activity.

Mechanisms of treatments

Palomino summarized known mechanisms of *Polypodium leucotomos* action on the skin which underlie its photoprotective action, including that in vitiligo patients.PubMed

Methodological advancements

Kim et al.PubMed suggested fixation of suction blister epidermal grafting in surgical treatment of vitiligo with fibrin glue, and demonstrated feasibility of the approach on two patients, with fibrin glue seemingly improving graft fixation and providing protection against infection and better conditions for wound healing. Ashique & KaliyadanPubMed reported on a reference (all-in-one) image demonstrating outcome of suction blister formation in vitiligo surgery, and Kim et al.PubMed described a follicular unit extraction technique for repigmentation in vitiligo. Thatte & KhopkarPubMed presented data supporting better performance of dermoscopy compared to histopathological examination in a diagnosis of evolving vitiligo thus obviating a need for biopsy.

Shamsudin et al.PubMed used computerized digital system image analysis to objectively evaluate treatment response in vitiligo patients. Authors reported poor agreement between the method used and physician's global assessment, which is interpreted by authors as an indication to use investigated assessment method for objective analysis of re- or depigmentation.

Purschke et al.PubMed reported comparison of two novel methods to generate epidermal micrografts, with the method based on simultaneous harvesting of small blisters on dressing material found to be of choice, offering possibility to treat large areas with less donor site trauma.

Novel treatment modalities

Group of researchers leaded by Dr. Passeron showed that twice weekly topical tacrolimus can be successfully used to prevent relapse after successful repigmentation which occurs in ~40% of cases within the first year.PubMed This is the first attempt to develop preventive rather that therapeutic treatment for vitilgio.

Group of John Harris reported[PubMed] results of their study of simvastatin as a drug for vitiligo treatment in mouse model. They reported that simvastation was capable both prevent and reverse experimentally induced vitiligo and reduce skin infiltrated autoreactive cytotoxic T-cells. The foreseen place of simvastatin as a drug for vitiligo treatment awaits its confirmation in ongoing human clinical trail.

Zhang et al.[PubMed] investigated efficiency of Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG PSN), a potent immunomodulator, as an agent to treat vitiligo in combination with CO_2 laser. Superior efficiency has been observed compared to CO_2 laser treatment alone, with concomitant decrease in Th17 cell subset and IL-17/IL-23 levels reduction in peripheral blood, and IL17/IL-23 lesional expression, which might mechanistically explain better observed efficiency of experimental treatment.

Wang et al.[PubMed] discussed recently developed alternative to artificial phototherapy, a Photocil cream, which delivers 311 nm irradiation from sunlight to the skin upon topical application.

Clinical studies and trials

Anbar and coauthors[PubMed] reported results of a pilot study aiming to evaluate efficacy of topical prostaglandin F2α analogue latanoprost in the repigmentation of vitiligo lesions. Based on results from study on 22 patients with intrapatient comparison, authors concluded that topical latanoprost is as effective as NB-UVB phototherapy, and their combination is superior over either one alone. This report confirms results of few previous studies on potency of topically applied prostaglandins to induce repigmentation in vitiligo lesions.

Sun et al.[PubMed] presented systematic review of randomized controlled clinical trails of 308 nm excimer laser for vitiligo treatment, and concluded on its equal efficiency compared to excimer lamp and NB-UVB in terms of reaching >75% repigmentation.

Ebadi et al.[PubMed] evaluated benefits of adding eximer laser phototherapy after melanocyte-keratinocyte transplantation in vitiligo patches. In agreement with previous reports on combination of transplantation with phototherapy, pigmentation rate was increased.

Van Geel et al.[PubMed] compared intra- and interpatiently efficiency of cryotherapy and 755 nm laser treatment in inducing depigmentation in vitiligo patients, with the conclusion on similar efficiency of both depigmentation strategies.

Colluci et al.[PubMed] reported results of comparative study of vitiligo treatment with comparable topical agents or phototherapy either combined with oral supplementation with antioxidant complex (*Phyllanthus emblica* fruit extract, vitamin E and carotenoids) or not. In general, better repigmentation has been seen in experimental group along with less inflammation, disease progression and erythema. Thus oral antioxidant supplementation might have certain benefits in vitiligo treatment.

In a small (40 patients) clinical study Dr. Majid[PubMed] confirmed efficiency of targeted NB-UVB phototherapy with 31 (77.5%) responders with repigmentation ranging from 50% to 100% after 30 sessions, with best response seen in face and neck.

Al-Shobaili[PubMed] presented evaluation of QoL changes after treatment with excimer laser, and found that excimer laser treatment positively affects QoL of vitiligo patients, which previously has been acknowledged as an important measure of vitiligo treatment success and parallels reported physician's evaluated results of the treatment.

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