TITLE: Proceeding Report of the Second Vitiligo International Symposium (VIS)- November 9-10, 2018, Detroit, Michigan, USA

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ABSTRACT:
The 2nd Biennial Vitiligo International Symposium (VIS) was held in Detroit, Michigan, USA from November 9-10, 2018. This symposium was hosted by the Global Vitiligo Foundation (GVF). The purpose of this meeting was to provide a forum for the exchange of research ideas and discussion of results on basic science and clinical research on vitiligo, and to gather input from patients on advocacy efforts, quality of life, and perception of the disease. This meeting was attended by over 180 clinicians, researchers, and patients from North America, Central America, Europe, Africa, and Asia.

1 | Introduction

The Global Vitiligo Foundation (GVF) hosted the 2nd Biennial Vitiligo International Symposium (VIS) which was held at the Detroit Marriott at Renaissance Center in Detroit, Michigan, USA from November 9-10, 2018. The conference was opened by Iltefat H. Hamzavi (Detroit, Michigan, USA), President of the GVF and Co-Chair of the VIS and David M. Ozog (Detroit, Michigan, USA), C.S. Livingood Chair and Chairman of the Department of Dermatology of Henry Ford Hospital, Detroit, Michigan, USA. Henry W. Lim (Detroit, Michigan, USA), former President of the American Academy of Dermatology, Chair Emeritus of the Department of Dermatology of Henry Ford Hospital, and Co-Chair of the VIS, then presented highlights of the meeting. The meeting was organized around four plenary lectures, several diverse panel discussions, and workshops emphasizing vitiligo surgery and imaging.

Despite the increased awareness and dedicated research into the disease, there is still much to learn regarding pathophysiology, epidemiology, and management of vitiligo. The purpose of this meeting was to provide a forum for the exchange of research ideas and discussion of basic science and clinical research on vitiligo and to gather input on advocacy efforts, quality of life, and perception of the disease. Patients with vitiligo were also involved and attended a patient session. This meeting was well received by 184 attendees from 23 countries around the world. This manuscript reviews the topics discussed at the meeting.

2 | Plenary Lectures

Four plenary lectures explored the complex pathophysiology of vitiligo, future targets for therapy, and optimization of treatment outcomes.

- Julien Seneschal (Bordeaux, France) discussed the combination of genetic predisposition and environmental triggers leading to crosstalk between epidermal and immune cells in vitiligo. His work suggests that metabolic defects in melanocytes lead to activation of the immune response and initiation of vitiligo through several pathways involving the innate and adaptive immune response and that targeting of some of these pathways could be potential treatment options.

- Zafla Abdel Malek (Cincinnati, OH, USA) reviewed successful strategies to treat vitiligo were discussed including reducing melanocyte stress, regulating the auto-immune response, stimulating melanocyte regeneration, and maintaining melanocytes by survival factors. In addition, the role of oxidative stress in vitiligo pathogenesis, epidermal and dermal abnormalities in vitiligo skin, and the paracrine interaction of melanocytes, keratinocytes, and fibroblasts was reviewed.

- Qing-Sheng Mi (Detroit, MI, USA) reviewed the complex interactions between genetics, environment, and immune response with an emphasis on iNKT cells and Th17 cells. The immunopathogenesis of vitiligo was discussed with emphasis on new therapy targets as well as biomarkers for vitiligo activity and response to treatment.

- Somesh Gupta (New Delhi, India) discussed various lessons regarding transplantation in vitiligo including patient selection, maintenance therapy, tissue vs cellular grafting, cultured vs non-cultured suspensions, standardization of procedures, recipient site

preparation, complications and how to avoid them, and future directions. Disease stability as the "rate-limiting step" in transplantation in vitiligo was also emphasized.

3 | Panel Discussions and Poster Presentations

Updates on the pathophysiology, severity assessment tools, comorbidities, treatments, and surgical options for vitiligo were presented.

3.1 | Pathophysiology of Vitiligo

New insights into the pathophysiology of vitiligo were presented relating to keratinocyte behavior, detachment of melanocytes from the basal membrane, apoptosis of melanocytes, and progression of disease.

The discovery of the role of keratinocytes in the pathogenesis of vitiligo is a relatively new advancement in the understanding of the disease. Kovacs et al (Rome, Italy) presented work that showed the presence of alterations in the architecture and functionality of keratinocytes in normal appearing skin in vitiligo patients when compared to those without vitiligo. This underlines the fact that in vitiligo, there is involvement of all cutaneous cell populations. In addition, Esmat (Cairo, Egypt) showed that keratinocytes in vitiligo patients show abnormalities in adhesion, apoptosis, and cytokine production. Aquaporins play an important role in keratinocyte differentiation and adhesion, and Aquaporin 3 is defective in vitiligo lesions.

The detachment of melanocytes is also a major factor in disease development. Boniface (Bordeaux, France) proposed a new mechanism to explain melanocyte loss in which inflammatory cytokines act directly on melanocytes to downregulate E-cadherin expression and increase production of MMP9 by epidermal cells which leads to subsequent detachment and loss of melanocytes from the basal layer and suggested that MMP9 inhibitors could contribute to melanocyte stabilization. Similarly, Gautier (Bordeaux, France) suggested that defective adhesion of melanocytes could play a crucial role in vitiligo pathogenesis. This theory is that stress promotes detachment of a melanocyte into the dermis (melanocytoptosis) where it is engulfed within a macrophage, carried by a dendritic cell, and presented to a T-cell to initiate the autoimmune T-cell mediated killing of melanocytes.

The apoptosis of melanocytes is also thought to contribute. Passeron (Nice, France) discussed the activation of CXCR3B on melanocytes and its role in induction of their apoptosis. Thus, targeting CXCR3B could prove to be a new therapeutic target. In addition, Oh (Seoul, South Korea) presented information on high mobility group box 1 (HMGB1), a chromatin protein, and its association with melanocyte apoptosis and vitiligo pathogenesis. Manga (New York, New York, USA) discussed the dysfunctional stress response pathways and their role in vitiligo development and melanocyte survival. Three survival pathways were identified and included the unfolded protein stress response, the NRF2-regulated antioxidant response, and the nuclear factor-kappa B (NFkB) pathway.

Markers for progression of vitiligo were also presented. Boniface (Bordeaux, France) found that perilesional skin in progressive vitiligo patients shows up-regulation of NKG2D when compared to stable vitiligo and control patients. This highlights NKG2D as a potential marker for progression which could be targeted for therapeutic management options. Additionally, advances

in the role of metabolism were discussed by Bastonini (Rome, Italy) whereby there is intrinsic metabolic impairment involving the cells of both dermis and epidermis in vitiligo patients. Melanocytes in vitiligo patients overexpress mitochondrial genes and autophagic markers. In addition, Muhammad (Cairo, Egypt) found that increased serum IL-23 levels might have a role in pathogenesis of vitiligo through the initiation of inflammation. Patients with active vitiligo had significantly higher serum IL-23 levels than controls whereas stable vitiligo patients did not have a significant difference in IL-23 levels when compared to controls.

3.2 | Assessing Vitiligo Severity

Numerous methods to evaluate vitiligo severity were presented including subjective and objective assessment tools. Abdallah (Cairo, Egypt) presented her work on the self-administered vitiligo extent score (SA-VES) which demonstrated excellent feasibility (easily comprehensible, easily administered, and short completion time) in an Egyptian population and showed validity with physician's Vitiligo Extent Score (VES). The first guide for interpretation of the numerical output obtained by the SA-VES with translation into a global vitiligo severity grade was then presented by van Geel (Ghent, Belgium). She also presented the interrater reliability of a Physician Global Assessment (PGA) tool. Lui (Vancouver, BC, Canada) reviewed the well-established Vitiligo Area Scoring Index (VASI) which was developed to quantify the objective visible appearance of vitiligo on the skin and reflect specific aspects of the clinical disease presentation including the overall area of involvement and the gradual nature of repigmentation (i.e. freckling, repigmentation from the border, or homogeneous repigmentation). He also discussed noninvasive optical analysis using multimodal spectroscopy of vitiligo which reveals additional potential pathophysiologic changes beyond the absence of melanin from the skin.

Methods to more accurately measure small changes in surface area involvement were also presented. Zubair (Detroit, MI, USA) presented the fingertip unit (FTU) whereby 1 hand unit equivalent to 1% body surface area (BSA), and 1 FTU corresponds to 0.03% BSA. Vickers (Philadelphia, PA, USA) introduced a novel technique using a smartphone application to perform surface area measurements allowing for more objective tracking of changes over time.

3.3 | Vitiligo Treatments

Results of clinical trials and studies on vitiligo treatments were presented. Passeron (Nice, France) presented the results of a double-blind placebo-controlled trial of apremilast in combination with narrowband UV-B (NBUVB) vs NBUVB alone for vitiligo which showed that repigmentation was not statistically significantly different between the two groups.

Depigmentation study results were also presented. Majid (Srinagar Kashmir, India) presented results from a long-term study with follow-up of 4 years which found that Q-switched Nd: YAG laser treatment is an effective tool for treating residual pigmentation in universal vitiligo, and the effect can be maintained with regular sunscreen use and topical depigmentation therapies as needed. Similarly, Mostafa (Cairo, Egypt) showed that depigmentation of residual normal skin using monobenzyl ether of hydroquinone (MBEH) can greatly improve quality of life in patients with extensive vitiligo.

3.4 | Comorbidities

The predisposition for other autoimmune conditions in patients with vitiligo is well known. Other comorbid conditions have been less studied. Bae (Gyeonggi-do, South Korea) presented work from the Korean NHI Claims database which revealed that pregnant women with vitiligo had a significantly lower rate of full-term pregnancy and a higher incidence of spontaneous abortion when compared to pregnant women without vitiligo. In addition, compared to vitiligo patients with no NBUVB phototherapy, those with greater than 100 sessions had reduced risks of cardiovascular events, cerebrovascular events, and all major osteoporotic fractures. Nguyen (Huntington Beach, CA, USA) presented results from a sample of 67 patients with vitiligo and showed there was no relationship between vitiligo and obesity. Grimes (Los Angeles, CA, USA) presented results from a recent study which revealed that vitiligo patients had significantly higher vitamin D levels compared with other skin diseases. Additionally, Seneschal (Bordeaux, France) showed that the presence of increased IgE levels in patients with vitiligo is negatively associated with other autoimmune processes and is associated with Koebner Phenomenon type 1. Thus, surgical procedures for vitiligo in these patients with elevated IgE levels should be weighted carefully with the risk of depigmentation at the donor site.

Bhatia (Detroit, MI, USA) presented information from vitiligo support groups which revealed that photoprotection habits and understanding of the effects of UV light on vitiligo differs significantly between patients who participate in support groups versus those who do not. Patients with vitiligo who were in support groups had safer sun protection habits and declared less often to believe that sun exposure leads to increased risk of skin cancer in vitiligo patients. Additionally, Smith (Detroit, MI, USA) presented data that vitiligo support group members are more likely to report a higher psychosocial burden and worse quality of life than non-support group members.

3.4 | Surgical Options for Vitiligo

Numerous surgical options for vitiligo were discussed with emphasis on different techniques as well as patient selection. Non-cultured melanocyte keratinocyte transplantation (MKTP) pioneered by Mulekar (Mumbai, India) has many advantages over other surgical methods for vitiligo and gives excellent cosmetic results in most of the treated cases. Recently, many indicators of good and bad prognoses with MKTP have been observed. Fingertip involvement and large areas of vitiligo are worse prognostic factors. In addition, children respond more poorly compared to adults. Altalha (Riyadh, Saudi Aradia) reviewed the main causes of relapse in patients treated with MKTP including fingertip involvement as well as disease instability. In addition, mechanical dermabrasion had decreased relapse rates when compared to laser dermabrasion of the recipient area. Ahmed (Worcester, MA, USA) presented findings of autoreactive CD8+ T-cells which remain present in clinically stable vitiligo patches. This could explain the relapse or poor surgical response with different vitiligo subtypes after cell or tissue transplantation. Given this, pre and post-operative phototherapy or immunosuppressive medical therapy might improve success after surgery.

Other surgical methods were also described. Gupta (New Delhi, India) compared non-cultured epidermal cell suspension and non-cultured extracted hair follicle outer root sheath cell suspension and found that both provide comparable results in terms of repigmentation despite less cells being transplanted in the outer root sheath cell suspension. Majid (Srinagar Kashmir, India) described the technique of smash grafting which can serve as an alternative to cellular

grafting techniques in resource poor settings. In addition, smash grafting can repigment a recipient vitiligo lesion that is 5-10 times the size of the donor graft. Punch grafting is another commonly used technique. The skin seeding technique described by Min Bae (Gyeonggi-do, South Korea) using a 0.5mm punch showed excellent treatment results for stable vitiligo refractory to medical treatment regardless of the direction of the punch grafting orientation. A study by Atwa (Ismailia, Egypt) found that needling has no significant effect on the outcome of punch grafting and in some cases, might have a worse outcome leading to less repigmentation and higher incidence of a depigmented rim. In contrast, Benzekri (Rabat Maroc, Morocco) found that transepidermal melanocyte delivery via dermarolling/dermastamping with needles is a simple, safe, and effective therapeutic option for nonacral, stable vitiligo patches not exceeding $100cm^2$.

Melanocyte count and viability were also reviewed. Esmat (Cairo, Egypt) presented data that both the gluteal and thigh region are equally suitable for harvesting donor tissue for surgery due to similar melanocytic count in both areas. In addition, the melanocyte count was significantly increased in both sites after 18 sessions of NBUVB phototherapy. In addition, El-Hawary (Cairo, Egypt) found that for the treatment of stable vitiligo lesions, modified autologous cultured hair follicle outer root sheath cell suspension transplantation compared to autologous non-cultured hair follicle cell suspension transplantation showed more melanin content and melanocyte viability. However, this modified autologous cultured hair follicle outer root sheath cell suspension transplantation method is more expensive and time consuming than the non-cultured method.

4 | Workshops

Several specialized workshops were held during the meeting including an interactive surgical workshop, an imaging workshop, and a patient session.

- A surgical workshop for vitiligo took place at the Department of Dermatology, Henry Ford Hospital. This surgical workshop was coordinated by Iltefat Hamzavi (Detroit, MI, USA) and Richard Huggins (Detroit, MI, USA). Lectures were given by vitiligo experts from different countries regarding tissue and cell transfer surgical approaches to vitiligo treatment. Following didactics, a live demonstration of MKTP was conducted; the attendees observed the surgery in real time.

- A vitiligo imaging workshop also took place during the conference. Standardized photography, ideal illumination source, and automated segmentation for vitiligo imaging were discussed. In addition, a summary of the previous imaging meeting in Paris, France as well as future directions for work were reviewed.

- The VIS hosted a patient session for patients with vitiligo as well as family members. This session was an opportunity for patients and their loved ones to hear about vitiligo from experts and leading researchers in the field in language that the public could understand.

5 | Conclusion

The 2nd Biennial VIS provided a forum for dissemination of the most up to date vitiligo research from around the globe. Despite the knowledge gaps that are still present, this research will continue to advance our knowledge of the disease in order to work toward more affective treatment options. The authors wish to thank all of the attendees, presenters, and patients who attended the symposium.