Study Title: Early Molecular Changes in Vitiligo After Narrowband Ultraviolet Therapy

NCT No.: NCT03270241

04/12/2018

JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

****

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Vitiligo is a chronic acquired inflammatory skin disease reportedly affecting approximately 1% of the world's population. Patients with vitiligo often experience emotional disabilities that can severely impact their quality of life. There have been several studies that demonstrate the negative impact that vitiligo has on quality of life, which are comparable to other chronic skin diseases like atopic dermatitis, psoriasis, and acne. While the exact etiology of vitiligo is unknown, both the humoral and cellular immunity are believed to contribute to the pathogenesis of the disease. Histological and molecular differences are also observed between normal and vitiligo skin. Currently, narrow-band UVB (NB-UVB) irradiation, is the most common medical therapy available for vitiligo. NB-UVB has been observed to stimulate melanocyte migration and proliferation and exihibit immune-modulating effects.

Previous research studies observed that long-term NB-UVB phototherapy on vitiligo skin have demonstrated effectiveness and safety, both visually and molecularly. The current study aim to evaluate the molecular and histological impact of short-term NB-UVB treatment. We will perform patient and clinical evaluations along with skin biopsies from normal and vitiligo skin. We hypothesize after one week of NB-UVB treatment, there will be observable molecular changes in vitiligo-treated skin when compared to vitiligo untreated and normal skin.

2. Objectives (include all primary and secondary objectives)

Primary Objective: To evaluate the molecular changes from NB-UVB in Vitiligo treatment
Secondary Objective: To identify potential targets for further study and for treating Vitiligo.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Vitiligo is a chronic acquired inflammatory skin disease reportedly affecting approximately 1% of the world's population (Kyriakis KP et al, 2009; Taieb A, 2007). Vitiligo remains primarily a clinical diagnosis ad can be made with the help of the Wood's lamp, which is a handheld Ultraviolet (UV) irradiation device that emits UVA waves at 365 nm. The Wood's lamp can be particularly

helpful in determining the extent of vitiligo and assess the response to therapy (Gawkrodger DJ et al, 2008). Additionally, histopathology can confirm the diagnosis, usually showing few or absence of melanocytes and a sparse inflammatory cell infiltrate (Kim YC et al, 2008).

Patients with vitiligo often experience emotional disabilities that can severely impact their quality of life. There have been several studies that demonstrate the negative impact that vitiligo has on quality of life, which are comparable to other chronic skin diseases like atopic dermatitis, psoriasis, and acne. (Kent G et al, 1996; Radtke MA et al, 2009; Talsania N et al, 2010; Ongenae K et al, 2009; Linthorst Homan MW et al, 2009; Parsad D et al, 2003) The most commonly applied metric is the Dermatology Life Quality Index (DLQI), a widely accepted and validated dermatology-specific patient quality of life assessment. This questionnaire consists of 10 questions evaluating social and functional impairments related to skin disease, based on a score ranging from 0 (no impairment) to 30 (severe impairment). (Finlay AY et al, 1994) Vitiligo has also been associated with psychiatric morbidity which can translate to significant psychosocial burden and functional disabilities. (Sampogna F et al, 2004; Mattoo SK et al, 2002; Mattoo SK et al, 2001) The Skindex-29 provides another validated quality-of-life metric that may address more of the emotional and psychosocial impact of the skin disease and has been applied in few vitiligo studies. (Ahmed A et al, 2013; Linthorst Homan MW et al, 2009)

While the exact etiology of vitiligo is unknown, the autoimmune hypothesis is the most supported. Both humoral and cellular immunity may contribute to the pathogenesis of the disease. Non-specific antibodies to the cell surface and intracellular pigment and non-pigment cell antigens have been found in the sera of the vitiligo patients. There had been evidence that melanocytes may be preferentially more susceptible to the immune-mediated injury than the other cell populations in the epidermis, keratinocytes and fibroblasts, ultimately leading to the vitiligo phenotype (Bystryn JC, 1989; Norris DA et al, 1988). Moreover, the increased levels of melanocyte-specific auto-reactive CD8+T cells that seem to correlate with disease severity have been shown in the peripheral blood of the vitiligo patients (Ogg GS et al, 1998; Palermo B et al, 2001; Lang KS et al, 2001). Recently, mouse models for vitiligo demonstrate that these auto-reactive T cells produce interferon gamma (IFN-gamma), which may be a crucial component to the migration and accumulation of the melanocytes-specific CD8+ T cells (Harris JE et al., 2012).

Histological and molecular analysis of vitiligo show impaired and absence of melanocytes, supported by molecular changes, such as the absence of KIT receptor, a protein expressed early in melanocyte differentiation, in vitiligo patients (Gokhale BB and Mehta LN, 1983). Perivascular inflammatory cell infiltrates have also been observed. Additional molecular difference between normal and vitiligo skin include decrease of stem cell factor (SCF), and increase levels of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1) (Lee AY, 2012).

Genetic factors also have found to impact vitiligo. Epidemiologic studies in Caucasian families support that vitiligo is inherited in a non-Mendelian, multifactorial, polygenic pattern with incomplete penetrance (Alkhateeb A et al, 2003). Most cases of vitiligo are sporadic although familial clustering is not uncommonly seen.

Currently, reversing vitiligo depigmentation treatments, such as phototherapy psoralen plus ultraviolet (PUVA) and Narrow band UVB (NB-UVB) irradiation, is the most common medical therapy available for vitiligo. UVB phototherapy refers to the use of artificial UVB radiation in the treatment of medical conditions without the addition of exogenous photosensitizers. The radiation absorbed by endogenous chromophores, and the photo-chemical reactions involving these biomolecules mediate a variety of biological pathways, ultimately leading to the therapeutic effects. The mechanism of action of NB-UVB is not fully clear although in vitro studies provide support

that phototherapy stimulates melanocyte migration and proliferation and exhibit immune-modulating effects (Wu CS et al., 2007, Nishimura EK et al., 2002 and Chou WC et al., 2013). NB-UVB has also shown to promote repigmentation by inducing tyrosinase, an enzyme involved in melanin production, and increasing the presentation of HMB-45 marker on the surface of melanosomes (De Francesco V et al, 2008). Goldstein B et al., 2015 observes that vitiligo skin that received NB-UVB treatment of 3-6 months bring depigmented skin to normal status with no difference in melanocyte marker expression between treated and normal skin.

In addition, NV-UVB phototherapy is FDA-approved for both in-office and at-home treatment of vitiligo. The efficacy of NB-UVB phototherapy has been demonstrated in clinical studies, with heterogeneity among the trials with respect to disease severity, percent of body surface are affected, skin type, treatment, compliance, and outcome measures. In the 1997, Westerhof et al., first demonstrated that NB-UVB is effective in treating vitiligo. Most of the clinical studies on NB-UVB in vitiligo incorporated a comparator treatment group; rarely were there studies that compared NB-UVB with placebo in the treatment of vitiligo. Nevertheless, NB-UVB was found to be effective as monotherapy for vitiligo lesions and essentially a non-drug treatment that can be administered to patients quickly and safely (Yashar et al, 2003; Natta et al, 2003; Hamzavi et al, 2004; Kanwar et al, 2005; Parsad D et al, 2006; Bhatnagar et al, 2007; El-Zawahry BM et al, 2012).

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).
b. Study duration and number of study visits required of research participants.
c. Blinding, including justification for blinding or not blinding the trial, if applicable.

d. Justification of why participants will not receive routine care or will have current therapy stopped.
e. Justification for inclusion of a placebo or non-treatment group.
f. Definition of treatment failure or participant removal criteria.
g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

This is an investigator-initiated, single-blinded, localized ascending dose study of NB-UVB treatment for vitiligo in adults of 3 treatments for one week. It is designed to measure the molecular changes and repigmentation in affected and normal skin of participants with vitiligo and normal skin in healthy participants. The study will collect questionnaire information, patient and clinical evaluations, and skin biopsies from each participant.

For all enrolled subjects, the starting dose will be 250 mJ/cm^2, which is the standard of care for patients with vitiligo. The dose will be increased by 10% with each treatment, as long as there are no side effects with treatment such as burning or redness/ erythema. Skin biopsies will be collected from normal skin and from affected skin from vitiligo patients, and from normal skin of healthy patients at the baseline visit and up to 1 week after the conclusion of treatment; up to a total of 6 biopsies will be collected from each patient. Collected tissue samples will undergo subsequent pathological examination or laboratory analysis. Recording of the initial treatment dose and the 10% increase in dosing per visit is tracked. All data collection is secured and stored in locked office of our Cutaneous Translational Research Program (CTReP).

Recruitment: Individuals will be recruited from the patient population seen at the general dermatology clinics of Johns Hopkins Department of Dermatology or from the patient population participating in Johns Hopkins Cutaneous Translational Research Program (CTReP) research studies. Potential participants will also be recruited if they are referred by other providers. Patients referred from other providers will have been asked their interest in learning more about the study and will have given their permission to be contacted by a study team member for more information. Participants will also be recruited from other patient populations at the Johns Hopkins Hospital and/or surrounding community through the use of advertisements. Interested individuals will be interviewed either in-person or over the telephone to see whether they meet basic eligibility criteria to participate in the study (see inclusion/exclusion criteria). Once eligibility has been demonstrated, the potential subjects will be directed to make their study appointment with an investigator.

Up to 20 healthy and vitiligo-diagnosed adult participants will be recruited. Interested, eligible participants will be invited to the initial visit, which will take place at the Cutaneous Translational Research Unit located at the Johns Hopkins Outpatient Center. At this appointment, to be conducted in a private exam room, the potential participant will be consented to participate in the study, for the collection of photographs, for administration of questionnaire, for an assessment of their skin, for phototherapy, and for skin biopsies. Prior to NB-UVB treatment, baseline biopsies will be obtained from normal and affected skin sites of vitiligo patients and normal skin of healthy patients. NB-UVB treatment will be administered on selected skin areas by research personnel. Patient will receive two additional NB-UVB treatments within the same week to total 3 treatments in a week, a typical schedule used in the treatment of vitiligo. Up to a week after the last treatment, biopsies will be obtained from treated skin regions. About 10 days after the biopsy, patient will return for suture removal.

Questionnaire: A questionnaire on basic demographic information and past dermatologic history will be administered to subjects by CTReP investigators. Subjects will also be able to complete the questionnaire by themselves. Questionnaire data will be coded and stored on a secure hard drive managed by the CTReP staff.

Device: The 3 Series PC & SP phototherapy cabinet is a microprocessor controlled full body fluorescent ultraviolet light source, with spectral output at peak wavelength of 311 nm (Narrow Band UVB). It is intended for use by or under the direction of a physician, for the treatment of psoriasis, vitiligo, and atopic dermatitis (eczema). The desired dose is selected using the operator interface located on the front panel of the device. The 3 Series delivers full body phototherapy, whereby fluorescent tubes, which surround the patient, deliver the specified dose of UVB.

Photographs: Digital photographs will be obtained by study staff of each participant, at skin regions of vitiligo and normal skin, such as the extremities and trunk that are receiving treatment and areas of biopsy. Photograph files will be stored on a secure hard drive in the CTReP.

Skin biopsies: Up to six 4mm-punch biopsies will be performed at normal skin region and from treated vitiligo lesions for vitiligo patients or at normal skin for healthy patients: up to 3 biopsies will be obtained from each subject prior to NB-UVB treatment and up to 3 biopsies will be obtained up to one week after the last treatment. Biopsies will undergo subsequent pathological examination or laboratory analysis to assess for molecular change and repigmentation.
The punch biopsy is a routine dermatological procedure consisting of local anesthesia with 1% lidocaine, followed by the punch which cuts a cylindrical core of epidermis, dermis, and

subcutaneous tissue. After removal of the tissue sample, a 4-0 suture is placed to close the circular opening on the arm (5-0 suture is used on the face). Ten days after the procedure, the sutures are removed. A 3-4 mm scar is formed, but typically blends well with the surrounding skin and becomes difficult to appreciate.

Laboratory studies: Microscopic and/or immunohistochemical studies may be conducted on pathology slides obtained from biopsy specimens, and photographs of pathology slides may be taken. Biopsy specimens may also be molecularly evaluated for protein and gene expression. Remaining tissue material may be anonymously stored for use in future studies. Using collected skin biopsy samples, various biochemical markers of phototherapy-induced or other cellular characteristics may be studied. Examples may include expression of melanocyte and keratinocyte markers, and migration of cells within the intra-epidermal and sub-epidermal regions.

Objective Assessment/ Evaluation: Objective assessment of protein and gene expression will be conducted as above. The investigators performing the molecular testing will be blinded to the disease status and treatment status of the tissue.

5. Inclusion/Exclusion Criteria

Inclusion Criteria

- Adults 18 years or older with bilateral symmetrical vitiligo lesions, in general good health as determined by the Principal Investigator by medical history and physical exam.
- Able to understand consent procedure
- Able to comply with protocol activities

Exclusion Criteria

- Patients less than 18 years old
- Patients not able to understand consent procedure
- Patients unable to comply with protocol activities
- Non-English speakers: the study assessments/questionnaires/evaluations are not scientifically validated in languages other than English. Given the lack of translators in over 50% of patient encounters in the dermatology clinic and the interpreters' limited time commitments when one does show up, it is impossible to safely enroll or follow patients who do not speak English. Phone translators are impossible given that we have written consent forms, which often exceed 10 pages in length.
- Patients with a photosensitive disorder or on a medication which has been demonstrated in these patients to cause photosensitivity
- Patients receiving concomitant phototherapy to test sites
- Patient receiving topical medication to test sites within 2 weeks of study initiation
- Patient receiving oral medications for vitiligo within 4 weeks prior to study initiation
- Receipt of an investigation agent within the past 4 weeks (or within 5 half lives) prior to study initiation
- Pregnant or nursing patients (self-reported)
- Patient with significant medical history or concurrent illness that the investigator feels is not safe for study participation, including melanoma
- Presence or suspicion of bleeding disorder or diathesis which would complicate biopsy.
- Patients with history of excessive scar or keloid formation in the past 10 years
- Patients with known allergy to anesthetic used

- Subjects with a pacemaker, implanted cardioverter-defibrillator, baroreflex activation device, cochlear implant, implanted bone growth stimulator, robotic limb prosthesis, subcutaneous GPS tracking device, electrodes implanted in the brain, attached electrodes in a subject undergoing cardiac defibrillation during the moment of skin color reading, or other device which may be disrupted by electrical current, UNLESS subject is kept "1 yard (one arm's length) from the main unit" of the spectrophotometer at all times, as specified in device approval letter.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Device:

The study device: 3 Series PC & SP Phototherapy Cabinet, marketed by Daavlin Distributing Company, will be used in this study. The device's peak spectral output is Narrow Band UVB (NB-UVB): 311 nm. FDA Device Listing Number: 21 CFR 878.4630.

7. Study Statistics

a. Primary outcome variable.
b. Secondary outcome variables.
c. Statistical plan including sample size justification and interim data analysis.
d. Early stopping rules.

Results from completed questionnaires may be analyzed using statistical tests such as the unpaired t-test or the Mann-Whitney/Wilcoxon rank sum non-parametric test. Images of biopsy samples will be processed using Adobe Photoshop CS3 software. Laboratory results will be analyzed at the JHU Department of Dermatology to compare the molecular changes associated with phototherapy treatment of vitiligo for up to one week. Data from the various age groups and skin-types will be compared using tests such as ANOVA followed by Bonferroni correction for multiple comparisons.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
b. Steps taken to minimize the risks.
c. Plan for reporting unanticipated problems or study deviations.
d. Legal risks such as the risks that would be associated with breach of confidentiality.
e. Financial risks to the participants.

Local Anesthesia

The risk associated with local anesthesia (lidocaine with or without epinephrine) is very small and is mainly related to minor discomfort (typically an initial prick from the needle and then mild burning sensation from the medicine), possible bleeding, and a very small chance of infection or allergic reaction.

Skin Biopsy

During the biopsy, there should not be any pain, only pressure. There will likely be a small amount bleeding and, in very rare cases, infection at the site, and will result in a small linear scar (same length as the size of biopsy tool used) that typically heals without problem and fades over time.

NB-UVB Phototherapy

The reported side effects are: itching, burning, erythema, desquamation, transient hyperpigmentation, blistering, ulceration, and xerosis. There appears to be no increased risk for non-melanoma skin cancers or melanoma but all phototherapy modalities can induce photo-damage and photo-aging with prolonged use (Welsh O et al, 2009; Kanwar AJ et al, 2005; Chen GY et al, 2005; Hearn RM et al, 2008). Mild side effects can be treated by the application of emollients such as petroleum jelly (Vaseline), while increased severity of side effects requires discontinuation of the treatment, application of emollients or the application of topical steroids. As with all phototherapy devices, exposure to UV light, whether it is from the sun or from a device requires eye protection. Protective eyewear will be available in the office and the treatment unit.

Confidentiality

In terms of confidentiality, there are minimal risks associated with breach of confidentiality. There is slight financial risk to the participants in the rare event that the above complications occur requiring additional medical care.

9. Benefits

a. Description of the probable benefits for the participant and for society.

This study will be conducted in accordance with current U.S Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

Description of the probable benefits for the participant and for society:
Individual participant: NB-UVB phototherapy have been shown to improve skin conditions like vitiligo, thus it is very possible that the device can improve the participant's skin findings as well as quality of life. This, however, cannot be guaranteed and it is possible that there will be no direct benefit to any individual participant.
Society: There is potential for the enhanced understanding of the therapeutic effects of NB-UVB phototherapy on the treatment of vitiligo and optimizing a proposed treatment regimen using this modality.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Study participants will receive all treatments and frequent assessments by dermatologists free of charge but will receive a compensation of $30 for each biopsy.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Study costs will be completely borne by the Johns Hopkins Department of Dermatology.

12. Reference

Ahmed A, Leon A, Butler DC, Reichenberg J. Quality-of-Life Effects of Common Dermatological Diseases. Semin Cutan Med Surg 2013. 32: 101-9.

Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 2003. 16: 208-14.

Bhatnagar A, Kanwar AJ, Parsad D, De D. Psoralen and ultraviolet A and narrow-band ultraviolet B in inducing stability in vitiligo, assessed by vitiligo disease activity score: an open prospective comparative study. JEADV 2007. 21: 1381-85.

Bystryn JC. Serum antibodies in vitiligo patients. Clin Dermatol 1989. 7: 136-45.

Chen GY, Hsu MM, Tai HK, Chou TC, Tseng CL, Chang HY et al. Narrow-band UVB treatment of vitiligo in Chinese. J Dermatol 2005. 32: 793-800.

Chou WC, Takeo M, Rabbani P, et al. Direct migration of follicular melanocyte stem cells to the epidermis after wounding or UVB irradiation is dependent on Mc1r signaling. Nat Med. 2013;19:924–9.

De Francesco V, Stinco G, Laspina S, Parlangeli ME, Mariuzzi L, Patrone P. Immunohistochemical study before and after narrow band (311 nm) UVB treatment in vitiligo Eur J Dermatol 2008. 18: 292-6.

El-Zawahry BM, Bassiouny DA, Sobhi RM, Abdel-Aziz E, Zaki NS, Habib DF, Shahin DM. A comparative study on efficacy of UVA1 vs. narrow-band UVB phototherapy in the treatment of vitiligo. Photodermatol Photoimmunol Photomed 2012. 28: 84-90.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994. 19: 210-16.

Gawkrodger DJ, Ormerod AD, Shaw L, Mauri-Sole I, Whitton ME, Watts MJ et al. Guideline for the diagnosis and management f vitiligo. Br J Dermatol 2008. 159: 1051-76.

Golstein B, Koster M, Hoaglin L et al. Narrow Band Ultraviolet B Treatment for Human Vitiligo Is Associated with Proliferation, Migration, and Differentiation of Melanocyte Precursors j Invest Dermatol 2015 135(8): 2068-2076.

Gokhale BB, Mehta LN Histopathology of vitiliginous skin. Int J Dermatol 1983, pp. 477–480

Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, Turka LA. A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN- γ for Autoreactive CD8+ T-cell Accumulation in the Skin. J Invest Dermatol 2012. 132: 1869-76.

Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric Modeling of Narrowband UV-B Phototherapy for Vitiligo Using a Novel Quantitative Tool: The Vitiligo Area Scoring Index. Arch Dermatol 2004. 140: 677-83.

Hearn RM, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Br J Dermatol 2008. 159: 931-5.

Kanwar AJ, Dogra S, Parsad D, Kumar B. Narrow-band UVB for the treatment of vitiligo: an emerging effective and well-tolerated therapy. Int J Dermatol 2005. 44: 57-60.

Kent G, Al'Abadie M. Psychologic effects of vitiligo: a critical incident analysis. J Am Acad Dermatol 1996. 35: 895-8.

Kent G, Al'Abadie M. Factors affecting responses on Dermatology Life Quality Index items among vitiligo sufferers. Clin Exp Dermatol 1996. 21: 330-3.

Kim YC, Kim YJ, Kang HY, Sohn S, Lee ES. Histopathologic features in vitiligo. Am J Dermatopathol 2008. 30: 112-6.

Kyriakis KPO, Palamaras I, Tsele E, Michaildes C, Terzoudi S. Case detection rates of vitiligo by gender and age. Int J Dermatol 2009; 48: 328-9.

Lang KS, Caroli CC, Muhm A, Wernet D, Moris A, Schittek B et al. HLA-A2 restricted, melanocyte-specific CD8(+) T lymphocytes detected in vitiligo patients are related to disease activity and are predominantly directed against MelanA/MART1. J Invest Dermatol 2001. 116: 891-7.

Lee AY Role of Keratinocytes in the Development of Vitiligo. Ann Dermatol 2012. 2: 115-125

Linthorst Homan MW, Spuls PI, de Korte J, Bos JD, Sprangers MA, Wietze van der Veen JP. The burden of vitiligo: Patient characteristics associated with quality of life. J Am Acad Dermatol 2009. 61: 411-20.

Mattoo SK, Handa S, Kaur I et al. Psychiatric morbidity in vitiligo: prevalence and correlates in India. J Eur Acad Dermatol Venereol 2002. 16: 573-8.

Mattoo SK, Handa S, Kaur I et al. Psychiatric morbidity in vitiligo and psoriasis: a comparative study from India. J Dermatol 2001. 28: 424-32.

Natta R, Somsak T, Wisuttida T, Laor L. Narrowband ultraviolet B radiation therapy for recalcitrant vitiligo in Asians. J Am Acad Dermatol 2003. 49: 473-76.

Nishimura EK, Jordan SA, Oshima H, et al. Dominant role of the niche in melanocyte stem-cell fate determination. Nature. 2002;416:854–60.

Norris DA, Capin L, Muglia JJ, Osborn RL, Zerbe GO, Bystryn JC et al. Enhanced susceptibility of melanocytes to different immunologic effector mechanisms in vitro: potential mechanisms for postinflammatory hypopigmentation and vitiligo. Pigment Cell Melanoma Res 1988. 1: 113-23.

Ogg GS, Rod Dunbar P, Romero P, Chen JL, Cerundolo V. High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo. J Exp Med 1998. 188: 1203-8.

Ongenae K, Van Geel N, De Schepper S, Naeyaert JM. Effect of vitiligo on self-reported health-related quality of life. Br J Dermatol 2005. 152: 1165-72.

Palermo B, Campanelli R, Garbelli S, Mantovani S, Lantelme E, Brazzelli V et al. Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major

histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. J Invest Dermatol 2001. 117: 326-32.

Parsad D, Kanwar AJ, Kumar B. Psoralen-ultraviolet A vs. narrow-band ultraviolet B phototherapy for the treatment of vitiligo. JEADV 2006. 20: 175-77.

Parsad D, Pandhi R, Dogra S, Kanwar AJ, Kumar B. Dermatology Life Quality Index score in vitiligo and its impact on the treatment outcome. Br J Dermatol 2003. 148: 373-4.

Radtke MA, Schafer I, Gajur A et al. Willingness-to-pay and quality of life in patients with vitiligo. Br J Dermatol 2009. 161: 134-9.

Sampogna F, Picardi A, Chren MM, Melchi CF, Pasquini P, Masini C, Abeni D. Association between poorer quality of life and psychiatric morbidity in patients with different dermatological conditions. Psychosom Med 2004. 66: 620-4.

Taieb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res 2007; 20: 27-35.

Talsania N, Lamb B, Bewley A. Vitiligo is more than skin deep: a survey of members of the Vitiligo Society. Clin Exp Dermatol 2010. 35: 736-9.

Welsh O, Herz-Ruelas ME, Gomez M, Ocampo-Candiani J. Therapeutic evaluation of UVB-targeted phototherapy in vitiligo that affects less than 10% body surface area. Int J Dermatol 2009. 48: 529-34.

Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. Arch Dermatol 1997; 133: 1525-8.

Wu CS, Lan CC, Wang LF, Chen GS, Wu CS, Yu HS. Effects of psoralen plus ultraviolet A irradiation on cultured epidermal cells in vitro and patients with vitiligo in vivo. Br J Dermatol 2007. 156: 122-9.

Yashar SS, Gielczyk R, Scherschun, L, Lim HW. Narrow-band ultraviolet B for vitiligo, pruritus, and inflammatory dermatoses. Photodermatol Photoimmunol Photomed 2003. 19: 164-68.