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VITILIGO: A REVIEW OF ETIOLOGY AND ITS TREATMENT

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ABSTRACT

Vitiligo is an autoimmune condition affecting the skin that specifically targets melanocytes, the cells responsible for producing pigment, leading to areas of depigmentation that appear as white patches. Recent research has significantly advanced our understanding of the mechanisms underlying this disease. Autoreactive cytotoxic CD8+ T cells interact with melanocytes and drive disease progression by producing IFN-γ locally, which in turn prompts surrounding keratinocytes to secrete IFN-γ-induced chemokines, further attracting T cells to the skin in a positive-feedback manner. Treatments, both topical and systemic, that inhibit IFN-γ signaling have proven to be effective in reversing vitiligo in patients; however, recurrences are frequent once treatment is discontinued. The recurrence is attributed to autoreactive resident memory T cells, and novel therapeutic approaches are being developed to eliminate these cells for lasting benefits. This article reviews various basic, translational, and clinical studies that shed light on the pathogenesis of vitiligo and how this knowledge has informed the development of new targeted therapies. Vitiligo results from the damaging or malfunctioning of melanocytes, the cells that generate melanin, and is thought to stem from intricate interactions among genetic, autoimmune, and environmental factors. While vitiligo does not pose a direct threat to life, it can profoundly affect an individual's psychological and social well-being due to its noticeable appearance. Treatments involve topical corticosteroids, phototherapy, skin depigmentation, and newer therapies aimed at either restoring pigmentation or slowing disease progression. Despite continued research, a definitive cure remains elusive, and the focus of management is on enhancing the quality of life for those affected.

KEYWORD: Vitiligo, Etiology, Classification of Vitiligo, Signs, Symptoms, Diagnosis, Treatment, Recent advancement.

HISTORY OF VITILIGO

Vitiligo has been documented for 3,500 years in texts from Egypt and India, highlighting the social stigma associated with this disfiguring condition from its earliest mentions. The Atharvaveda, an ancient Indian text dating between 1500 and 1000 BCE, makes reference to white patches on the skin, as does the Egyptian Ebers Papyrus (1500 BCE) and the book of Leviticus in the Hebrew Bible from around the same period. Literature from India suggests that marrying someone with these white patches was widely disapproved of.

Early Buddhist texts indicated that individuals with vitiligo were ineligible for ordination, while Hindu writings implied that those afflicted by this condition may have committed theft in their past lives.

Ancient History

1. Ancient Egypt

Vitiligo was acknowledged by ancient Egyptians, who included mentions of it in their medical writings. The condition was sometimes referred to as "white patches" on the skin. Certain artworks from ancient Egypt depict individuals with skin color changes, which may indicate the existence of vitiligo.

2. Ancient India

In Indian literature, especially within Ayurvedic practices, vitiligo is known as "Shwitra" or "Leucoderma." Ayurveda associates it with a disruption of the body's essential forces (doshas). Early treatments consisted of herbal remedies, changes in diet, and lifestyle modifications.

3. Ancient Greece and Rome

Vitiligo was noted by Greek physician Hippocrates (c. 460–370 BC) in his texts. He proposed that the condition could stem from an imbalance in the body, though his explanations were not thoroughly developed. Roman physician Celsus (c. 25 BC – 50 AD) also mentioned the disease, reflecting an early comprehension of the relationship between skin coloration and health.

Key Milestones in the History of Vitiligo

Ancient periods: Skin discoloration was acknowledged in writings from Egypt and India.

1. 16th century: The term "vitiligo" was derived from Latin.
2. 19th century: An autoimmune theory was suggested.
3. 20th century: Treatments began to emerge, including UV light therapy and corticosteroids.
4. 21st century: Progress has been made in genetics, immunology, and innovative therapies.

Vitiligo remains a vibrant field of study, and as researchers uncover more about its genetic and autoimmune roots, there is hope for the development of more effective treatments and enhancement of life quality for those affected.

INTRODUCTION

Vitiligo is marked by irregular skin depigmentation that can occur anywhere on the body. It impacts about 1% of the global population, with no significant variations in incidence based on sex, ethnicity, or geographical location. As in ancient times, vitiligo adversely affects the quality of life for patients, diminishing self-esteem and causing considerable psychological turmoil. This decline in quality of life is similar to that seen in other debilitating skin conditions like psoriasis and eczema. The visible signs of vitiligo lead to feelings of embarrassment, anxiety, and depression. Areas

that are more noticeable, such as the face and hands, are often the most impacted, and patients frequently express concern about the progression and worsening of their condition in these visible regions.

Ongoing misconceptions and negative social perceptions related to vitiligo continue to affect individuals living with the condition. One of my patients (J.E.H.), who traveled to our clinic by plane, experienced a woman requesting to change her seat because of his vitiligo, even after he reassured her that it was not contagious. Another woman with vitiligo encountered a child on the subway in New York City who remarked, “You look like a monster, but I know you’re not!” A man from Pakistan, now residing in the UK, expressed the desire to amputate his arm to eliminate his vitiligo, fearing family rejection due to the condition which he believed could be avoided if he were missing a limb. Therefore, fostering a deeper understanding of the disease's origins could lead to more effective treatments and significantly benefit those affected by vitiligo.

Research has demonstrated the existence of oxidative stress in cultured melanocytes, along with an increased vulnerability to oxidative agents. In living organisms, oxidative stress has been linked to the significant accumulation of H2O2 in vitiligo-affected skin, which correlates with decreased activity of catalase and glutathione peroxidase.

Given that many oxidative stress-related chronic conditions are classified as degenerative diseases, we explored the possibility that melanocytes in vitiligo exhibit characteristics similar to cells involved in neurodegenerative disorders. For a majority of such diseases, it has been shown that mild oxidative stress and the resulting cellular changes — including alterations in lipid metabolism, dysfunction in the mitochondrial respiratory chain, disruption of intracellular signaling, and increased sensitivity to pro-apoptotic signals — contribute to aging and cellular degeneration. Additionally, a premature senescence-like phenotype has been associated both in vivo and in vitro with degenerative illnesses. Some cells in aging organisms lose their functionality; for instance, neurons lose the capacity to form synapses while their cell bodies remain viable.

In this report, we provide strong evidence that melanocytes in vitiligo exhibit alterations in signal transduction pathways at both cellular and molecular levels, indicating a stress-induced premature senescence-like phenotype that supports categorizing vitiligo as a degenerative disease.

Furthermore, biopsies of non-lesional skin in vitiligo patients demonstrated that findings from cell culture studies were not artificially induced by the culture environment and validated the emergence of a p53-dependent pro-senescent phenotype.

Recently, it was discovered that the nuclear factor E2-related factor 2 (Nrf2), a key system for antioxidant enzymes, along with its target genes, shows increased levels in biopsies of non-lesional skin from vitiligo patients. This indicates that a consistently elevated transcriptional activity dependent on Nrf2 is necessary to maintain redox homeostasis in the skin that appears disease-free. Supporting the notion that vitiligo skin experiences ongoing intracellular oxidative stress, an increase in p53 protein has been observed in both lesional and non-lesional epidermis of individuals with vitiligo.

Psychosocial Impact

Vitiligo can significantly affect individuals emotionally and psychologically. Its visible symptoms may cause feelings of self-consciousness, diminished self-esteem, and anxiety. Additionally, it can influence social interactions and result in discrimination or stigma in certain cultural or community contexts. Participating in support groups and receiving counselling can help those facing the emotional struggles associated with vitiligo.

Outlook

Vitiligo is a chronic condition that generally does not impact one's physical health, but it can considerably affect an individual's quality of life, particularly if the condition spreads or worsens. Early intervention and treatment may assist in managing symptoms, and research continues to seek more effective therapies and a potential cure for vitiligo.

In conclusion, vitiligo is a multifaceted condition with both physical and emotional dimensions.

ETIOLOGY

1. Autoimmune Mechanism

The prevailing theory regarding vitiligo is that it is autoimmune in origin. In this model, the immune system erroneously targets and eliminates melanocytes, which are the cells responsible for melanin production in the skin. This immune response might be initiated by a combination of genetic and environmental elements.

Genetic Factors: A family history of vitiligo suggests a genetic link. Specific genes related to immune response modulation (such as HLA genes) have been associated with a heightened risk of developing vitiligo.

Environmental Triggers: Factors such as stress, trauma, sunburns, or exposure to chemicals (including phenolic compounds) can either trigger or exacerbate vitiligo in individuals who are genetically predisposed.

2. Genetic Factors

Vitiligo appears to have a familial tendency, indicating a genetic vulnerability. Numerous studies have pinpointed certain genes related to an increased likelihood of this condition, particularly those associated with immune regulation (e.g., NLRP1, CTLA-4, PTPN22, and VITILIGO-related genes). Nonetheless, no individual gene has been identified as the sole cause of vitiligo, suggesting that various genetic aspects are involved in its onset.

A study involving twins indicated that identical twins (monozygotic) have a higher probability of developing vitiligo compared to non-identical twins (dizygotic), further emphasizing the genetic influence.

3. Neurohumoral Mechanism

This concept proposes that neurochemical substances released from the nerve endings in the skin could impact melanocytes, either leading to their malfunction or destruction. For instance, norepinephrine and various neuropeptides may play a role in melanocyte vitality, with stress-induced hormonal fluctuations potentially worsening the condition.

4. Oxidative Stress

Oxidative stress arises when there is a disruption between free radicals and antioxidants in the body. In the context of vitiligo, an increased formation of free radicals within the skin may harm melanocytes, resulting in pigment loss. Several studies have indicated that markers of oxidative stress are heightened in individuals with vitiligo.

5. Self-destruction of Melanocytes (Intrinsic Defects)

Another theory posits that melanocytes in those with vitiligo could have inherent defects that render them more vulnerable to damage. This vulnerability might stem from mutations in genes unique to melanocytes, leading to an inability to survive under normal circumstances.

6. Autoinflammatory Mechanisms

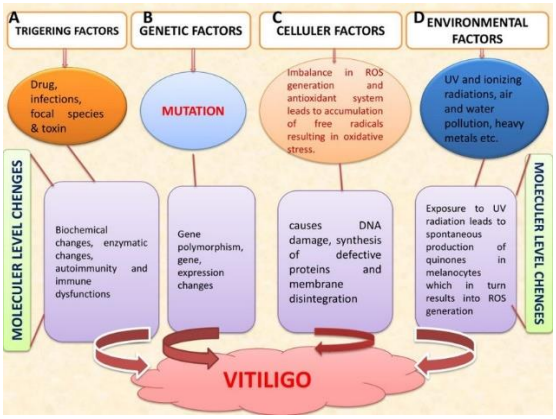
Inflammatory cytokines such as TNF-alpha and interleukins are believed to play a role in the development of vitiligo. These molecules may incite the recruitment of immune cells that target melanocytes, aiding in the depigmentation process.

7. Role of Other Factors

Infections: Certain viral infections (like herpes and rubella) have been suggested as possible triggers, although this relationship remains a matter of debate.

Endocrine Diseases: There is an observed correlation between vitiligo and autoimmune endocrine conditions such as thyroid disease, Addison's disease, and type 1 diabetes, indicating a shared autoimmune basis.

Dietary Factors: Shortages in specific vitamins or minerals (notably Vitamin D, B12, and folic acid) have been speculated to contribute to the condition, although definitive evidence is lacking.

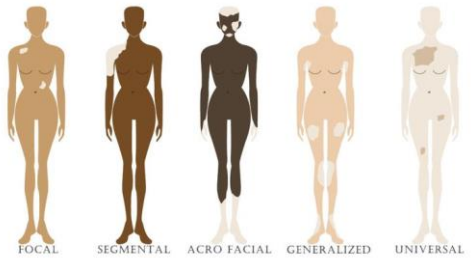


CLASSIFICATION OF VITILIGO

Vitiligo has been categorized primarily into two main types based on clinical features: segmental vitiligo (SV) and non-segmental vitiligo (NSV).

Subsequently, several variants were added, including generalized vitiligo, acrofacial vitiligo, and universal vitiligo. Non-segmental vitiligo generally develops over time, in terms of both its distribution and extent. This holds true for focal vitiligo, which may transform into SV, NSV, or remain unclassifiable according to the NSV/SV classification diagram. For NSV, the condition may start off classified as acrofacial but can later progress to a more accurate classification of generalized or universal. On the other hand, some NSV cases may avoid affecting the extremities (generalized non-acrofacial vitiligo). Certain NSV instances display a preference for flexural areas, while others tend to target extensor surfaces, implying varied triggers or underlying causes. Recently, mixed vitiligo (MV) has been identified as the coexistence of initial SV.

Type of vitiligo	Subtypes	Remarks
Non-segmental (NSV)	(Focal), mucosal, acrofacial, generalized, universal	Subtyping may not reflect a distinct nature, but it is useful information for epidemiologic studies
Segmental (SV)	Focal, mucosal, uni segmental, bi- or multi segmental	Further classification according to distribution pattern is possible, but not yet standardized
Mixed (NSV+SV) Unclassified	According to the severity of SV Focal at onset, multifocal asymmetrical non-segmental, mucosal (one site)	Usually, the SV part in mixed vitiligo is more severe This category is meant to allow, after a sufficient observation time (and if necessary investigations), to make a definitive classification



Reference: 2010 Classification (Taieb and Picardo, 2010)

OBJECTIVES OF VITILIGO RESEARCH

The following are some goals of research focused on vitiligo:

1. Investigating the Cause and Pathophysiology:

A primary goal of vitiligo research is to explore the fundamental causes, including genetic influences, autoimmune processes, and environmental factors, that contribute to the depigmentation of the skin.

2. Creating More Effective Treatments

Research is directed towards the development of innovative and more efficient therapies, such as targeted treatments, biologics, and gene therapies, which may restore pigmentation or slow the progression of the disease.

3. Early Diagnosis and Monitoring

Scientists aim to discover biomarkers that facilitate early diagnosis, in addition to tools that can track disease progression and evaluate treatment effectiveness.

4. Psychosocial Impact

Another essential goal is to comprehend the psychological and emotional effects of vitiligo so that healthcare providers can better support the mental health aspects of the condition.

5. Personalized Medicine

The focus is shifting towards tailored treatments that consider the patient's genetic and immunological characteristics to enhance efficacy and reduce side effects.

6. Promoting Melanocyte Regrowth

The approach to treatment varies based on factors such as the severity of vitiligo, activity of the disease, and specific subtype. A board-certified dermatologist can develop a treatment protocol to achieve these objectives.

MATERIAL AND METHODS

Cell culture

VHM were obtained from skin biopsies taken from normally pigmented areas in the gluteal or armpit regions. The subjects (6 females, 8 males) were aged between 7 and 56 years (mean age 38.6 years). NHM were collected from healthy individuals (8 females, 8 males) who had undergone plastic surgery, with ages ranging from 15 to 75 years (mean age 50.1 years). The cells were cultured in an M254 medium, enhanced with Human Melanocyte Growth supplements (HMGS) (Cascade Biologics, Mansfield, UK) and were utilized between passages 2 and 8. Approval from the Institutional Research Ethics Committee (Istituti Fisioterapici Ospitalieri) was obtained to collect human samples for research. The principles of the Declaration of Helsinki were adhered to, and all patients provided written informed consent. The study involved one child participant, for whom parental consent was also secured.

Cell viability and proliferation

To assess cell proliferation, cells were incubated with M254 combined with HMGS or M254 alone for 24 hours, followed by treatment with N-acetyl-L-cystein (5 mM) (Sigma Aldrich, Milan, Italy), or pifithrin-a (5 mM) (Santa Cruz Biotechnology, Santa Cruz, CA, USA). The medium was refreshed every 48 hours, allowing cells to grow according to the experimental design before conducting the Trypan blue exclusion assay. For cell viability testing, cells were exposed to t-BHP for 24 hours and subsequently incubated with 3-(4,5 dimethylthiazol)-2,5 diphenyl tetrazolium bromide (MTT) (Sigma Aldrich) for 2 hours. Afterward, the medium was discarded, and the resultant crystals were dissolved in DMSO. The absorbance was recorded at 570 nm with a reference wavelength of 650 nm.

Western blot analysis

Cell extracts were prepared using RIPA buffer with protease and phosphatase inhibitors. Proteins were separated on SDS-polyacrylamide gels, transferred onto nitrocellulose membranes, and then probed with antibodies for p53, SOD2, catalase, PML, and GADD45 (Santa Cruz Biotechnology, USA). Anti-b tubulin (Sigma Aldrich) was utilized to standardize protein content. Secondary antibody complexes conjugated with horseradish peroxide were detected using chemiluminescence (Santa Cruz Biotechnology).

Cholesterol membrane content analysis

Lipids were extracted twice using a chloroform: methanol mixture (2:1) along with butylated hydroxytoluene to act as an antioxidant and 5α-cholestane as an internal standard, followed by centrifugation at 1800 rpm for 10 minutes. The

lower phase was then evaporated under a nitrogen stream. Oxysterol esters underwent hydrolysis using 1M KOH in methanol. The consolidated organic extracts were evaporated under nitrogen flow and subsequently subjected to silylation with N,O-bis-(trimethylsilyl) trifluoroacetamide, which had 1% trimethylchlorosilane included as a catalyst. A temperature gradient ranging from 180°C to 250°C at a rate of 20°C/min was employed in the oven. Mass spectra were obtained using Electronic Impact and in SIM mode. The separation utilized a capillary column HP-5MS (30 m × 0.250 mm × 0.25 µm, Agilent Technologies INC) with helium serving as the carrier gas. The results are represented as a percentage ± SD, with NHMs content considered as 100.

Evaluation of intracellular reactive oxygen species

Reactive oxygen species (ROS) production was evaluated by incubating cells with the fluorescent dye 2979-dichlorodihydrofluorescein diacetate (Sigma Aldrich, Milan) for 30 minutes at 37°C and under 5% CO2 in darkness. After incubation, cells were washed with PBS, trypsinized, centrifuged at 1000 rpm, and then resuspended in PBS. The signals were quantified using flow cytometry (BD Bioscience).

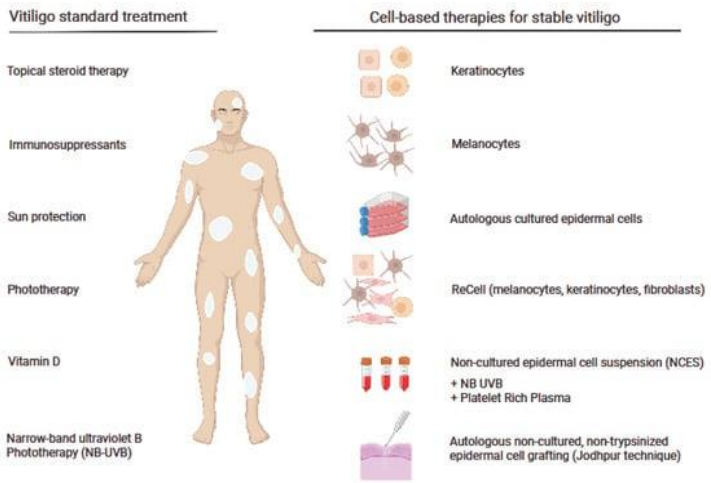


Fig. 1: Standard and cell-based therapies for vitiligo.

SIGNS AND SYMPTOMS

Vitiligo is a skin disorder that results in the loss of pigment-producing cells (melanocytes) in specific regions of the skin. The signs and symptoms can differ in intensity and appearance, but the following are the main characteristics generally observed in individuals with vitiligo:

1. **Depigmented Patches**

- Key Indicator: The defining feature of vitiligo is the emergence of white or light-colored patches on the skin.
- These patches typically lack symmetry and can manifest on any part of the body; however, common sites include the face, hands, arms, feet, and areas around openings such as the eyes, mouth, and genitals.
- The patches might begin as small spots but can gradually increase in size over time.
- The borders of the patches may be distinct, and they often occur in regions that are commonly exposed to sunlight or experience friction (e.g., elbows, knees, etc.).

2. Depigmentation on Mucous Membranes

- In certain situations, vitiligo can also impact mucous membranes, such as the inner mouth or genital area, causing a loss of pigment in these locations.

3. Premature Greying of Hair

- Hair: In areas affected by vitiligo (like the scalp, eyebrows, eyelashes, or facial hair), the hair may become gray or white due to the absence of melanin.
- This change can happen even in younger individuals.

4. Sensitivity to Sunlight

- Due to the lack of melanin in the affected skin areas, these patches are more vulnerable to sunburn. The depigmented regions may be prone to burning quicker than the surrounding skin.

5. Inflammation (in Early Stages)

- Initially, the skin surrounding the depigmented patches may appear red or inflamed during the early stages of the condition, often signifying an active phase.

6. Itching or Pain (Less Common)

- Some individuals might experience slight itching or burning sensations around the affected areas, though this is not universally experienced.

7. Leukotrichia

- In cases of vitiligo, hair in the depigmented regions can also lose its color, resulting in white or gray hair (a phenomenon referred to as leukotrichia).

8. Psychosocial Impact

- Though not a direct symptom, many individuals with vitiligo suffer psychological strain due to the visible nature of their condition, which can lead to anxiety, depression, and social stigma. The aesthetic implications can considerably impact one's self-esteem.

9. Other Potential Associated Features

- Vitiligo may occasionally coexist with other autoimmune disorders, including:
- Thyroid issues (either hypothyroidism or hyperthyroidism).
- Type 1 diabetes.
- Alopecia areata (spotty hair loss).
- Pernicious anemia.
- Addison's disease (adrenal insufficiency).

10. Pattern of Spread

- The progression of the condition can be unpredictable. Some individuals may develop only minor patches, while others may experience extensive depigmentation.
- It may advance over time or remain constant for several years.

11. Pigment Loss in Other Body Parts

- Eyebrows and Eyelashes: Hair in affected areas, like the eyebrows and eyelashes, may become depigmented, resulting in white or gray hair. This is often observed in the more advanced stages of vitiligo.
- Beard Area: Men may experience loss of color in facial hair due to depigmentation in the beard region.

12. Leukoderma (Whitening of Skin)

- In certain individuals, vitiligo can result in complete whitening of the skin in the affected areas, referred to as leukoderma.

13. Changes in Skin Texture

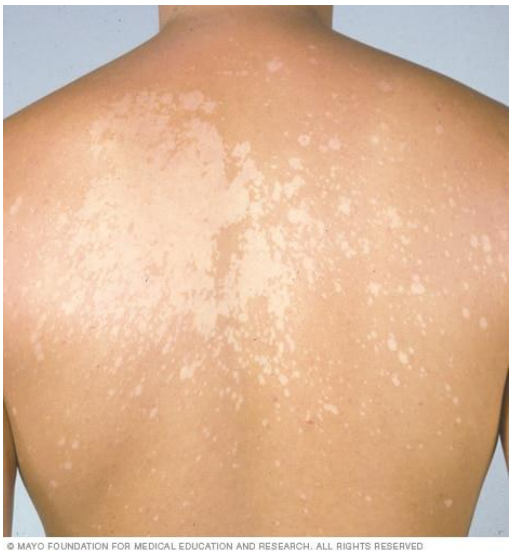
- In some cases, vitiligo may be associated with subtle alterations in the texture of the affected skin.

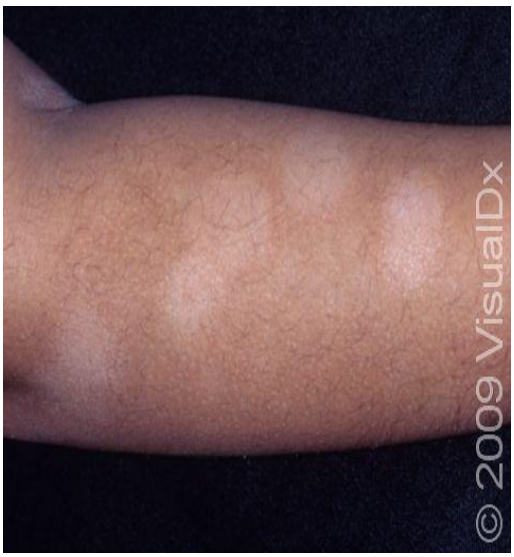
Fig. 1: Tinea versicolor.

Fig. 2: Pityriasis alba.

DIAGNOSTIC CRITERIA

DIFFERENTIAL DIAGNOSIS





DIAGNOSTIC CRITERIA

1. Clinical Assessment

The initial step in diagnosing vitiligo is a comprehensive physical assessment. The following characteristics are observed:

White skin patches: These patches are generally symptomless (not itchy or painful), often appearing in sun-exposed areas such as the hands, face, and around the eyes and mouth, but they can develop anywhere on the body.
Symmetry: The patches often develop symmetrically on both sides of the body, although this is not always true.
Depigmented skin: The patches are usually lighter than the surrounding skin, and the skin may remain smooth without any textural changes.

2. Medical Background

An extensive medical history is crucial to ascertain:

- Age of onset: Vitiligo can manifest at any age but is most frequently observed in young adults (ages 10-30).
- Family history: Since vitiligo can run in families, any family history of this condition or other autoimmune diseases is pertinent.
- Triggering factors: In some instances, stress, trauma, sunburn, or other environmental triggers may activate or worsen vitiligo.

3. Wood's Lamp Examination

This is a straightforward, non-invasive procedure that helps to make depigmented areas more visible:
Procedure: The patient undergoes examination under a specific ultraviolet (UV) light known as a Wood's lamp.
Appearance: Under the Wood's lamp, vitiligo's depigmented patches usually appear a brighter white or fluorescent, aiding in differentiating them from other conditions such as pityriasis alba or fungal infections.

4. Skin Biopsy (Optional)

Though not always required, a skin biopsy can assist in confirming the diagnosis and ruling out alternative conditions. The biopsy may reveal:

- Lack of melanocytes in the affected regions of skin (indicative of vitiligo).
- Normal skin with absent melanocytes along the periphery of the depigmented areas. However, this biopsy is more frequently utilized when there is ambiguity in the diagnosis or if another skin condition is suspected.

5. Laboratory Tests

Evaluation for autoimmune disorders: Vitiligo has associations with other autoimmune illnesses such as thyroid disorders (Hashimoto's thyroiditis, Graves' disease), diabetes, and pernicious anemia. Blood tests may include thyroid function assessments, ANA (antinuclear antibody) tests, and additional tests based on the symptoms.

TREATMENT

There are numerous treatment alternatives available for individuals with vitiligo. Most therapies aim to restore skin pigmentation. Each treatment approach presents its own set of benefits and drawbacks. No single treatment is suitable for every individual with vitiligo.

Sunscreens

Sunscreens aid in preventing sunburn and consequently reduce photodamage, which lowers the likelihood of an isomorphic response of Koebner. Furthermore, sunscreen minimizes tanning of unaffected skin, reducing the contrast with vitiliginous lesions.

Cosmetics

Many patients consider cosmetic cover-ups to be an effective treatment choice. Areas of skin depigmentation, particularly on the face, neck, or hands, can be concealed using standard make-up, self-tanning solutions, or other topical coloring agents. The benefits of cosmetics include low cost, minimal side effects, and ease of application. For children and adults with skin types I and II, it may be advisable to initially use no active treatment apart from cosmetics and sunscreen (level of evidence 4).

Topical Corticosteroids

Topical steroids are recommended for treating localized areas of vitiligo and are typically the initial treatment choice for pediatric patients, though most information available is anecdotal. Lesions occurring on the face tend to show the most favorable response, while those on the neck and limbs, excluding the fingers and toes, also respond positively. The reasons behind the superior response rate for facial lesions remain unclear. Theories suggest that facial skin may allow corticosteroids to penetrate more effectively, contain a higher concentration of residual melanocytes in surrounding unaffected skin, offer larger follicular reservoirs, or that melanocyte damage is more easily reversible. Facial lesions often re-pigment uniformly, while lesions in other areas typically show a dot-like, follicular re-pigmentation pattern.

A Wood's lamp examination can be utilized to assess treatment efficacy. If no improvement is observed after three months, the therapy should be stopped. Maximum re-pigmentation can take four months or longer (with a 30-40% response rate seen after six months of corticosteroid application). Patients with darker skin may experience a better response to topical corticosteroids compared to those with lighter skin tones. The advantages of using topical corticosteroids for limited vitiligo include ease of application, high compliance rates, and reasonable costs. However, recurrence after discontinuation and potential side effects of corticosteroids are notable disadvantages. All patients, particularly children, should be monitored closely for adverse reactions.

In both children and adults who have recently developed vitiligo, a potent or very potent topical steroid may be trialed for a maximum of two months (with a high level of evidence). Research by Kandil and Clayton indicates that while ultrapotent or potent topical steroids can lead to re-pigmentation in a small number of patients, the overall effectiveness is limited. Clayton discovered that 15-25% of re-pigmentation occurred in 10 out of 23 participants, and 75% in 2 out of 23. The remaining patients did not show any re-pigmentation. Kandil found that 90-100% of re-pigmentation occurred in 6 out of 23 subjects, with 25-90% in 3 others, while six patients exhibited “early pigmentation.” In cases with larger lesions in children and adults, a medium-potency non-fluorinated corticosteroid is often employed, generally with reduced efficacy.

Caution should be exercised when applying topical steroids around the eyelids as they may raise intraocular pressure and worsen glaucoma.

Topical Immunomodulators

Topical tacrolimus ointment (0.03-0.1%) has proven effective for re-pigmentation of vitiligo, especially when applied twice daily for localized cases, particularly on the face and neck. Tacrolimus ointment reportedly shows better results when used in conjunction with UV Borexcimer laser therapy. Generally, tacrolimus is deemed a safer alternative for children compared to topical steroids. For adults with symmetric vitiligo, topical pimecrolimus presents as an

alternative to topical steroids, exhibiting a more favorable side effect profile than highly potent topical steroids. This conclusion stems from a small study by Coskun and colleagues comparing topical pimecrolimus to clobetasol, which found pimecrolimus resulted in 50-100% re-pigmentation in 8 of 10 subjects. Similar outcomes were observed in 7 of 10 patients treated with clobetasol; however, no skin atrophy occurred in the pimecrolimus group, although some experienced mild burning as a side effect.

Topical Calcipotriol

In a randomized, open, left vs right comparison study conducted by Chiaverini, the impact of calcipotriol (0.005%) was evaluated in symmetric target lesions among 24 patients with localized and generalized vitiligo. After 3-6 months, no re-pigmentation was recorded in 21 of 23 patients, while one patient experienced 5% re-pigmentation and two others showed varying degrees of re-pigmentation both with and without calcipotriol.

Pseudo-catalase

It has been observed that vitiligo patients have reduced levels of catalase, an enzyme present in the skin that mitigates damage caused by free radicals. A therapeutic approach involving a catalase analog known as pseudo-catalase, paired with narrow-band UVB phototherapy, has shown potential in restoring pigmentation in some individuals with vitiligo and hinder the progression of the disease.

Systemic Therapies

The use of systemic immunosuppressive medications carries numerous potential side effects that may not be warranted for a condition like vitiligo. Nonetheless, systemic corticosteroids have been employed as pulse therapy with varying degrees of success and might help halt rapid depigmentation in active cases. In an open study by Radakovic-Fijan involving 25 adults with active generalized vitiligo treated with oral dexamethasone at a dose of 10 mg twice a week over 24 weeks, 22 out of 25 participants experienced an arrest in disease progression. Side effects occurred frequently and included weight gain, acne, menstrual irregularities, and excessive hair growth. Due to an unacceptable risk of adverse effects (level of evidence 2 A), systemic immunosuppressive agents are not recommended for managing vitiligo progression. A case report detailed re-pigmentation in a vitiligo patient undergoing treatment for psoriasis with efalizumab. While biologic treatments may present a possible option for vitiligo, their associated side effects might limit their application.

Phototherapy

The combination of topical or oral 8-methoxy psoralen with UVA radiation (PUVA) has proven effective in managing vitiligo, although multiple sessions over several months are necessary. After UVA exposure, psoralens bind covalently to DNA, impeding cell replication. The mechanism by which this promotes re-pigmentation of vitiligo lesions remains poorly understood. PUVA enhances tyrosinase activity and stimulates melanogenesis in unaffected skin, as well as exhibiting local immunosuppressive effects, with reduced expression of vitiligo-associated melanocyte antigens noted. In cases of vitiligo, melanocytes within the bulb and infundibulum of hair follicles are frequently destroyed, while the outer root sheath and the lower and middle sections of the follicle remain intact.

PRECAUTIONS

1. Sun Protection

Precaution: Individuals with vitiligo should shield their skin from sun exposure, as the depigmented areas are more vulnerable to sunburn and damage.

Action: Employ a broad-spectrum sunscreen with an SPF of 30 or higher, wear protective clothing (such as hats and long sleeves), and seek shade during peak sunlight hours.

2. Skin Moisturization

Precaution: Dry skin can exacerbate the appearance of vitiligo, causing discomfort and further irritation.

Action: Consistently apply a gentle moisturizer to maintain skin hydration and prevent dryness; opt for fragrance-free lotions to minimize irritation.

3. Avoid Skin Trauma

Precaution: Any skin injury, such as cuts, burns, or scrapes, may result in depigmentation or instigate new patches of vitiligo.

Action: Exercise caution to prevent physical trauma to affected areas. If an injury occurs, treat it delicately and refrain from scratching or irritating the skin.

4. Balanced Diet and Stress Management

Action: Ensure a well-rounded diet rich in antioxidants, vitamins (like Vitamin B12 and folate), and minerals. Managing stress through relaxation techniques (such as meditation or yoga) may also be beneficial.

Precaution: Although diet and stress do not directly cause vitiligo, they can worsen the condition.

5. Topical Treatments and Medical Interventions

Precaution: Over-the-counter products or treatments should be approached with caution, as some may irritate or aggravate the condition.

Action: Consult a dermatologist before initiating any treatment plan. Common options include topical corticosteroids, calcineurin inhibitors, and phototherapy.

6. Avoiding Contact with Harsh Chemicals

Precaution: Strong chemicals present in cosmetics, detergents, or cleaning supplies can irritate the skin and aggravate vitiligo.

Action: Utilize gentle, hypoallergenic skincare products and cleaning materials that are less likely to trigger irritation or allergic responses.

7. Psychological Support

Caution: Living with vitiligo may cause emotional distress or social stigma, potentially affecting one's quality of life.

Recommendation: Consider seeking therapy or participating in support groups to cope with the psychological impacts of vitiligo.

RECENT ADVANCEMENT

1. *JAK Inhibitors (Janus Kinase Inhibitors)*

Tofacitinib and Ruxolitinib have demonstrated potential in clinical trials as viable treatments for vitiligo. JAK inhibitors operate by inhibiting the inflammatory response of the immune system, which is thought to be a factor in the loss of melanocytes associated with vitiligo. Notably, Ruxolitinib received FDA approval in 2022 for topical application in vitiligo patients, showing significant re-pigmentation in clinical studies.

2. *Stem Cell Therapy*

Developments in stem cell therapies involve obtaining melanocytes from unaffected areas of a patient's skin or leveraging stem cells to encourage re-pigmentation in the vitiligo-affected regions. Ongoing research aims to improve the methods for transferring melanocytes to areas that have lost pigmentation. This strategy offers promising prospects for lasting re-pigmentation for individuals with stable vitiligo.

3. *Excimer Laser and Narrowband UVB Therapy*

Excimer lasers (308 nm) and narrowband UVB (NB-UVB) treatments remain foundational in managing the condition, but recent research highlights their improved effectiveness when paired with other treatments such as topical corticosteroids or photochemotherapy (PUVA). These methods facilitate re-pigmentation by boosting melanocyte growth.

4. *Targeted Biologic Therapies*

New treatments that target particular immune pathways, such as CTLA-4 and PD-1 inhibitors, have shown potential in reversing the autoimmune attack on melanocytes in vitiligo. These immune checkpoint inhibitors are already used in treating cancers like melanoma, and their prospective application for vitiligo is under investigation in clinical trials.

Improvement in a patient treated with JAK Inhibitor

CONCLUSION

Vitiligo is a complicated disorder with multiple contributing factors, and ongoing studies are shedding light on its underlying mechanisms, potential biomarkers, and more efficient treatments. The condition significantly affects the quality of life for those it impacts, highlighting the need for a comprehensive treatment strategy that integrates medical care with psychological support. Future developments in genetics, immunology, and innovative therapies show promise for enhancing the outcomes for individuals with vitiligo.

Key Takeaways

1. **Treatment Options:** While vitiligo currently lacks a definitive cure, various treatment methods—including topical therapies, phototherapy, skin depigmentation, and surgical procedures—can assist in managing the disorder and restoring some skin color.
2. **Personalized Approach:** Treatment efficacy differs from person to person, making it crucial to adopt a personalized strategy that accounts for the level of depigmentation, skin type, and individual preferences.
3. **Emotional Support:** Providing emotional and psychological support is vital in the management of vitiligo. Counselling services and support groups assist individuals in dealing with the social and emotional challenges associated with the condition.
4. **Ongoing Research:** Progress in medical research, especially in the fields of immunology and genetics, continues to enhance our comprehension of vitiligo and raises hopes for more effective treatment options in the future.
5. **Public Awareness:** Raising awareness about vitiligo can help diminish stigma and foster inclusivity, thereby creating a more understanding environment for individuals living with the condition.

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