A COMPREHENSIVE REVIEW ON VITILIGO AND IT’S TREATMENT

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ABSTRACT

The present review includes the study of vitiligo, its different types and disorder at the clinical, pathophysiological and therapeutic levels and also summarize the information gathered about treatments available of the vitiligo. Vitiligo, a depigmenting skin disorder, is characterized by the selective loss of melanocytes, which in turn leads to pigment dilution in the affected areas of the skin. Vitiligo occurs worldwide with an estimated overall prevalence of less than 0.5% in population-based studies. The causes are unknown but might be involved genetic factor, oxidative stress, autoimmunity, cellular effect, environmental factor etc. primary aim is to bridge current knowledge at the clinical and investigative level, to point to the many unsolved issues, and to delineate future priorities for research. Many treatment have been used for some time; however we provide an overview of the currently known herbal, homeopathic, allopathic, ayurvedic medicine and yoga treatment for vitiligo. The light therapy and surgical management has a very good tool for the vitiligo. The traditional treatment along with novel approaches of therapy to increase the quality of patient life.

KEYWAERDS: Vitiligo, Leukoderma, Topical drug delivery, Phototherapy, Pigmentation, Immune system.

INTRODUCTION

Vitiligo, a depigmenting skin disorder, is characterized by the selective loss of melanocytes, which in turn leads to pigment dilution in the affected areas of the skin. The characteristic lesion is a totally amelanotic, non-scaly, chalky-white macule with distinct margins. Considerable recent progress has been made in our understanding of the pathogenesis of
vitiligo, and it is now clearly classified as autoimmune disease, associated with genetic and environmental factors together with metabolic, oxidative stress and cell detachment abnormalities.\textsuperscript{[1,2]}

Vitiligo should not be dismissed as a cosmetic or insignificant disease, as its effects can be psychologically devastating, often with a considerable burden on daily life.\textsuperscript{[3]}

The reported prevalence rate is 1\% to 2\% of the population for both sexes and all races. Vitiligo is one of the best-known autoimmune diseases. Vitiligo has major effects on self-esteem and social life, and quality of life is highly impaired in patients with this disease.\textsuperscript{[4,5]}

At all ages, vitiligo can be psychologically devastating and considerably affect quality of life. Patients with vitiligo can be distressed and feel discriminated against because of their altered skin appearance. In some countries, vitiligo is confused with other diseases such as leprosy, and patients can be rejected from their community.\textsuperscript{[6]}

**History**

Vitiligo, the “small blemish” (From the latin vitulam ; Mercurial is 1572 ) was first described more than 1500 years BC. It is only in the last century that vitiligo vulgaris has been used to described the diseases process of acquired melanocyte destruction. The term vitiligo has been derived from the latin word “vitilus” meaning calf. Atharva Veda gives a description of vitiligo and many achromic or hypochromic diseases under different names such as “Kilasa”, “Sveta Khista”, “Charak”. The etymology of the term “vitiligo” is believed to be derived from “vitium” meaning “defect”. Neumann in Vienna (1880) and (1892) in Paris observed that emotional stress can lead to flare-ups of vitiligo.\textsuperscript{[7]}

**Epidemiology**

Vitiligo occurs worldwide with an estimated overall prevalence of less than 0.5\% in population-based studies. Some peaks of prevalence have been noted, especially in India, which may correspond to the still poor identification of environmental (but with a clear predominance of occupational factors) or genetic factors. Almost half the patients present before the age of 20 years, and nearly 70–80\% before the age of 30 years. Adults and children of both sexes are equally affected, although larger number of females consults the doctor probably due to the greater psycho–social perceived impact of the disease. Vitiligo
prevalence and incidence seem stable over time, at variance with allergic and autoimmune diseases.[8]

**Types of vitiligo**

There are different types of vitiligo, depending on how many patches someone has and where they are on the body.

1. **Mucosal vitiligo**
2. **Acrofacial vitiligo**
3. **Lip-Tip vitiligo**
4. **Focal vitiligo**
5. **Generalized vitiligo**
6. **Universal vitiligo**
7. **Inflammatory vitiligo**
8. **Trichome vitiligo**
9. **Contetti vitiligo**

1. **Mucosal vitiligo:-** Mucosal vitiligo shows vitiligo on the mouth and mucous membranes, including the genitalia. When whitish patches occur on the mucosae in isolation, especially on genital areas, lichen sclerosus should be differentiated. The mucous membranes of Caucasians are pink in colour and a loss of pigment is very difficult to detect, even with a Wood’s lamp Mucosal vitiligo affect the oral and/or genital mucosal vitiligo (MV). Pure MV is probably a distinct subset of this diseases.

![Figure 1: Mucosal vitiligo.](image-url)
2. **Acrofacial vitiligo**: Acrofacial vitiligo encompasses depigmentation of the distal parts of the extremities (hands rather than feet) and facial orifices, the latter in a circumferential pattern. The body surface areas contiguous to the initial sites usually show the highest rates of progression. However, when the hands are the initial site, vitiligo most commonly progresses to the face.

![Acrofacial vitiligo](image1)

**Figure 2: Acrofacial vitiligo.**

3. **Lip-Tip vitiligo**: Lip-Tip vitiligo evolves the area mostly the lips and fingers.

![Lip-Tip vitiligo](image2)

**Figure 3: Lip-Tip vitiligo.**

4. **Focal vitiligo**: Focal vitiligo is characterized the patches present in small area of the body, is called **focal vitiligo**. Focal vitiligo is a rare subtype of vitiligo and most patient have long lasting focal lesions after onset of diseases.
5. **Generalized vitiligo**: This type of vitiligo was widely known as vitiligo vulgaris, and is the most common form of the condition. A person has vitiligo patches all over the body and affect the right and left sides of the body in a symmetrical pattern. These are the common type, when macules appear in various places on the body.

6. **Universal vitiligo**: Universal vitiligo implies a loss of pigment over the entire body surface area, and complete or near-complete depigmentation can be noted. However, there are no criteria regarding the minimal percentage of body involvement of vitiligo for the diagnosis of universal vitiligo. It involves most of the body near about 80% of it, these is called universal vitiligo.
7. **Inflammatory vitiligo:**- The lesions could sometimes have a raised red border, but inflammation of numerous lesions at the same time is very uncommon. A mild pruritus could be associated. When the inflammation disappears, the skin is one of these very active forms, which has a pink border of the white spot, sometimes with some scale appearing there, and it’s often itchy.

8. **Trichrome vitiligo:**– It has three colours instead of two (“tri” means three, “chrome” means colour), including the normal skin, the white centre, and then a lighter hypopigmented border between the two. It remains to be clarified whether trichrome...
vitiligo is a temporary phenomenon of active-spreading vitiligo showing an unusual progression pattern.

Figure 8: Trichrome vitiligo.

9. **Confetti vitiligo:** It involves very small spots of vitiligo, usually 1-3mm in size, and found clustered form in larger areas, about the size of a quarter or around the edges of an exist. This type of vitiligo typically begin at early age and affect only one area on one side of the body.\(^{[9,10,11]}\)

Figure 9: Confetti vitiligo.

Figure 10: A special type of vitiligo.
A special type of vitiligo

There are three major types of vitiligo as follows:

- **Segmental Vitiligo**
- **Non-Segmental Vitiligo**
- **Mixed Vitiligo**
- **Segmental vitiligo**:- Segmental vitiligo is an uncommon form of localized vitiligo, characterized by dermatomal distribution. It is often unilateral and asymmetrical that never crosses the midline of body. Segmental vitiligo starts as well as stays in one side of body. SV is defined descriptively as for NSV except for a unilateral distribution (asymmetric vitiligo) that may totally or partially match a cutaneous segment such as a dermatome, but not necessarily. The term focal is preferred for a limited lesion i.e. where the affected patch is small (10–15 cm²) without an obvious distribution pattern. In this form of the disease, depigmentation spots spread quickly in the affected dermatomes and then stop growing.[12,13]

- **Non-Segmental vitiligo**:- NSV is an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes. As such, the definition is not specific enough; thus, it needs to be completed by a list of disorders which may clinically overlap with NSV (the acquired generalized hypo-melanoses), but which are clearly attributable to known etiologic factors. It is most common type of vitiligo observed in 90% cases.[14,15]

- **Mixed Vitiligo** - NSV and SV may coexist, and in this case SV lesions are usually more refractory to treatment, but mild segmental hypo-melanoses may co-exist with NSV. Such refractory SV lesions can be unmasked by phototherapy. This entity has probably been underreported until recently. Classification Issues Mixed Vitiligo intersection of both types in the rare cases where segmental becomes non-segmental.[16,17]

**Symptoms and Causes**

**Symptoms**

- Vitiligo varies in the amount of skin affect, with some patient experiencing few depigmented areas and other with loss of skin color.
- Few people say that skin affected by vitiligo itches and feels painful.
• Loss of color in the tissues that line the inside of your mouth and nose.
• The patches are irregular in shape, at times; the edges can become a little inflamed with a slight red tone.\textsuperscript{[18]}

Causes
Diseases in which the patient immune system attacks and destroys the melanocytes in the skin.
• Genetic factor (heredity).
• Neurogenic factor
• Self – destruction
• Due to sunburn and exposure to industrial chemicals

Diagnosis of vitiligo
Sometimes, immunohistochemical staining for melanocytes is needed for a differential diagnosis of vitiligo. Using specific antibodies, Kim et al. showed that their number was significantly decreased in vitiligo skin as compared with normal or nevus depigmentation skin, although melanocytes can exist in a small number of vitiligo lesions. So, the NKI/beteb and MART-1 immuno stains would be helpful to differentiate those lesions. With the FM stain it is possible to reveal the remaining melanin pigment, and the ratio of pigmented area to epidermal area.

If doctors need more information about the condition affects skin cells, they may suggest a skin biopsy or blood test.\textsuperscript{[19,20]}

Pathophysiology of vitiligo
1. Genetics of vitiligo
2. Oxidative stress
3. Innate immunity
4. Adaptive immunity
5. Environmental effect
6. Cellular effect

1. Genetics of vitiligo:- Genetic risk variants include melanocyte-specific alleles (tyrosinase, melanocortin 1 receptor, and OCA2), stress-associated genes (XBP1), and genes associated with innate immunity (NLRP1, TICAM1, IFIH1) and adaptive immunity (HLA-A, GZMB, IL2RA, and others), supporting the proposed roles of melanocyte
stress. This suggests that vitiligo may result from an over-reactive protective immune response against melanoma.\textsuperscript{[21]}

2. **Oxidative stress**: The early hypotheses, defined as auto-cytotoxic and neurogenic, have suggested that biochemical alterations leading to the intra or extracellular generation of free radicals and other toxic intermediates can induce melanocyte degeneration. Melanocytes are intrinsically exposed to high level of toxic compounds because during the melanin synthesis, potentially toxic intermediates are produced. In addition, melanocytes, due to their anatomical localization, are specifically exposed to UV irradiation and physical toxic agents.\textsuperscript{[22]}

3. **Innate immunity**: A second population of innate immune cells implicated in vitiligo pathogenesis is the inflammatory DC, reported both in lesion of human skin and blood, as well as in a mouse model of vitiligo. In summary, innate immune cells such as NK cells and inflammatory DCs may sense melanocyte stress and activate inflammation to initiate depigmentation in vitiligo.\textsuperscript{[23]}

4. **Adaptive immunity**: The primary effector cells of vitiligo are melanocyte-specific cytotoxic CD8\(^+\) T cells, which migrate into the skin, find their melanocyte targets, and destroy them. This was initially suggested by the presence of CD8\(^+\) T cells infiltrating lesional epidermis and their close proximity to dying melanocytes.

The cells included both CD4\(^+\) and CD8\(^+\) T cells, and a large number of the CD8\(^+\) T cells were melanocyte-specific and capable of killing melanocytes in vitro.\textsuperscript{[24]}

5. **Environmental effect**: The chemical, physical exposure frequent physical trauma or sun exposure may play a role in the appearance of vitiligo. Vitiligo Patients have a greater sensitivity to environmental stress and a lower threshold to generate catecholamine mediated responses. Phenolic/catecholic derivative are major chemical known to be associated with vitiligo since they are interfere in the melanin synthesis and induce oxidative stress. Other chemical mentioned as causative agent are nickle, chrome, cobalt, leather, hair dye cosmetic and cleansing products, all allergens that also cause allergic contact dermatitis by contact hypersensitivity (CHS).\textsuperscript{[25]}
6. Cellular effect:- Vitiligo is an autoimmune disease of the skin that results from cytotoxic T cell-mediated attack on melanocytes, the pigment-producing cells in the epidermis. The result is the loss of pigment in the skin, visible as white spots. Increased expression of intercellular adhesion molecule-1 (ICAM-1), HLA-DR and CD4 has been observed in active vitiligo lesions in comparison to controls and inactive lesions, but the expression of CD8 was not found to be different previously.\textsuperscript{[26]}

Treatment of vitiligo

1) Herbal treatment
2) Yoga treatment
3) Homeopathic treatment
4) Ayurvedic treatment
5) Allopathic treatment
6) Surgical therapies
   a) Autologus skin grafts
   b) skin grafts using blisters
   c) micropigmentation
   d) Cellular Grapts
   e) Autologus melanocytes transplant
7) Photochemotherapies
   A) PUVA therapy
      a) Oral PUVA
      b) PUVA sol
      c) Topical PUVA
      d) Khellin + UV
      e) Melagenine
   B) Phototherapy -
      a) Broadband UVA
      b) Broad-band UVB
      c) NB UVB
      d) Target phototherapy
      e) Lasers
      f) Non-laser light source
8) Additional therapies
a) Skin camouflage
b) Depigmentation
c) Cosmetic
d) Sunscreen
e) Topical treatment
f) Drug affecting immune system

1) Herbal treatment
Mechanism of the Herbs- it involves some mechanisms like phototoxic reactions, melanocyte proliferation, promoting anti-inflammatory activity and trigger reduction. Example-

a) Cucumismelo
Cucumismelo (also known as “Muskmelon”) is a species of Cucumis, plants of the Cucurbitaceae family. Cucumismelo extract is rich in antioxidants that naturally contain a high superoxide dismutase (SOD) activity, which has been proposed to be important in stopping the melanocytes deconstruction by the oxidative stress in the first step of vitiligo.\textsuperscript{27}

b) Khellin
Khellin is a naturally occurring furanochromone, derived from the plant Amnivisnaga. If the exact mechanism of action is unclear khellin acts by stimulating melanocytes proliferation and melanogenesis.\textsuperscript{28,29,30}

c) Other
Radish seeds powdered with the vinegar and paste is formed. Mixture of turmeric and mustard oil - prepared by heating two of them is also helpful in the treatment of white patch. Ginkgobiloba-acts as an anti-inflammatory, immunomodulatory, antioxidant properties of drug.\textsuperscript{31,32,33}

Advantages
1) Herbal plants are easily available and does not show any type of side effects.
2) Cost effective and convenience to use.

2) Yoga therapy
Yoga is effective in vitiligo. As yoga detoxifies the body & mind it is helpful to cope up with the condition of autoimmunity. There are different asanas which are really helpful with Ayurvedic treatment of vitiligo. All the Yoga poses and asanas are effective in developing
stamina and improving body immunity. Yoga exercises help to develop new cells and remove away the dead cells from the skin. If you perform yoga with techniques and under the supervision of an expert, there is a greater probability of regulating all the body parts of the body along with excess perspiration. It is the release of perspiration, which minimizes the occurrence of skin problems including leukoderma. List of Yoga for leukoderma cure - Meditation, Nadisodhana Pranayama, Bharamri Pranayama, Sitkari Pranayama, Sitali Pranayama, Kapalbhati, Savasana, Padmasana, Idhasana, Makrasana.\[34\]

**Advantages**

1) Yoga provide you a customized lifestyle.

2) It helps to get the body function on tract.

**3) Homeopathic treatment**

The primary outcome measure was to identify the usefulness of individualised homoeopathic medicine in the repigmentation of the patches and the secondary outcome measure was to identify a group of homoeopathic medicines in the management of the vitiligo. Homeopathy is an alternative medicine originated in Germany in 18th century. Arsach, Bacillinum, Graphites, Mercasol, Natmur, nuxvom, sil,sulph, thuja etc. medicines can be used under homeopathic treatment.

**Advantages**

1) No side-effects: Because homeopathic medicines are natural, they cause no side-effects unlike conventional medicines, which could cause severe burns and blistering.

2) No scarring: Unlike skin grafts, which could cause scarring, homeopathic sweet pills treat without scarring.\[35\]

**4) Ayurvedic treatment**

According to Ayurveda, Vitiligo or Shwitra is caused due to aggravation of Pitta in the body. Pitta is of five types. One of them is Bhrajak Pitta, which gives coloration to the skin. In the case of Vitiligo, Bhrajak Pitta gets imbalanced, leading to the formation of ama, which consequently impairs deeper body tissues such as rasa dhatu (nutrient from food), rakta (blood), mamsa (muscles) and lasika (lymph). This ultimately causes depigmentation of the skin. The disease is deep rooted and needs specific treatment that include right food and specialized herbal combinations to pacify Pitta and cleanse ama from the body, thereby treating the white spots and white skin for example.
Picrorhizakurroa:- Ayurvedic medicine had tried to treat vitiligo with herbal products, such as Picrorhizakurroa. Picrorhizakurroa (also known as “Kutki” or “Kutaki”) is another khellin extract. More recently, researchers have proposed how the herbal extract has antioxidant and immune-modulating activities too. Recently, a study investigated Picrorhiza Kuroda's potential use in association with phototherapy, in the treatment of vitiligo.\cite{36,37}

Capsaicin:- Capsaicin is one of the active component of chili peppers, plants of the genus Capsicum. Because its antinflammatory and antioxidant properties, the drug has been proposed as a therapeutic tool for vitiligo treatments.\cite{38}

Advantages
1) Ayurvedic principle for the safe and effective of the vitiligo.

5) Allopathic treatment
Vitamin D - If your skin is not exposed to the sun, there's an increased risk of vitiligo. Sunlight is the main source of vitamin D, although a form of vitamin D is also found in some foods, such as oily fish. It might be difficult to get enough vitamin D from food and sunlight alone. You should therefore consider taking a daily supplement containing 10 micrograms (mcg) of vitamin D. A GP will tell you how to apply the cream or ointment to the patches and how much you should use. You usually need to apply the treatment once a day. Pimecrolimus and tacrolimus are unlicensed for treating vitiligo, but they can be used to help restore skin pigment in adults and children with vitiligo.\cite{39}

6) Surgical therapies
Goal of vitiligo surgery- To achieve complete re-pigmentation that cosmetically matches the surrounding normal skin. Transfer melanocytes (pigment-producing cells) from normal skin (the donor site) to the skin affected by vitiligo. Surgical treatment for vitiligo can be considered in main categories to overcome the lack of response in many patients to pharmacological and UV-treatments a number of surgical techniques have been developed. The condition should be stable before surgery is performed. Surgical transplantation is the fastest way of restoring a loss of pigment cells.\cite{40}

a) Autologous skin grafts:- In skin grafting, a section of the skin of variable size and thickness is detached from its blood supply and donor site and placed on a new recipient site. The skin graft can be either a split-thickness or a full-thickness graft. The outcome of
skin grafts depends on their thickness. In the context of vitiligo, either thin split-thickness (Thiersch-Ollier) grafts or ultra-thin grafts (also known as epidermal sheets or epithelial grafts) are employed. First, and most importantly, the graft that is transplanted onto the derma braded vitiligo lesion does not stay permanently on the recipient area and is shed after a period of 7–14 days. This is followed by a gradual re-pigmentation of the recipient skin. Second, the graft is totally devoid of any dermal tissue which is gauged by the translucency of the graft.\textsuperscript{[41,42]}

b) Skin grafts using blisters:– These blisters can be induced with the help of vacuum or liquid nitrogen. At the dermo-epidermal junction the mechanical split occurs and the graft is secured on the recipient site. Primarily a cobblestone appearance and limited treatment area per session are the limitations of the above two mechanisms.\textsuperscript{[43]}

c) Micropigmentation:– Micropigmentation Principle The deposition of an exogenous inert pigment, such as ferric oxide, into the superficial papillary dermis can provide a prolonged camouflage of vitiliginous lesions.\textsuperscript{[44]}

d) Cellular grafts:– Cellular grafting techniques include non-cultured epidermal (melanocyte–keratinocyte)cell suspension, cultured epidermal cell suspension, cultured 200 melanocyte suspension, and non-cultured extracted hair follicle outer root sheath cell suspension (NCORSHFS) However, caution must be exercised when reviewing the literature as epidermal cell suspensions are sometimes reported as a keratinocyte cell suspension or melanocyte- rich cell suspensions. The potential advantage of techniques based on cell separation and/or culture is to allow the treatment of larger lesions than techniques based on whole tissue.\textsuperscript{[45]}

e) Autologus melanocytes transplant:– Vitiligo Type - The best indications are a stabilized segmental or focal vitiligo. It has an advantages over conventional split thickness grafting as it requires very little donor skin surface area treated.

Localization of Lesions - Transplanting immigrants to vitiliginous areas on the fingers has been described to be successful, but the success of re-pigmentation in these areas decreased when split-thickness grafts or epidermal blister roofs were used. Difficult- to-treat areas are joints, lips, eyelids, genitals, cutaneous folds, dorsum of hands and feet, especially the fingers and toes.\textsuperscript{[46]}
7) **Photo(chemo)therapy**

A) **PUVA therapy**:- Psoralen photochemotherapy with a combination of the furocoumarin psoralen (P), either ingested or topically applied, and UVA irradiation is known as PUVA. Such treatment with natural sunlight and topical psoralens dates back to ancient times. El Mofty was the first to perform careful clinical studies, however, and reported the successful regimentation of vitiligo with oral 8-methoxypsoralen (8-MOP).\[47]\n
a) **Oral PUVA**

Only patients with extensive vitiligo are considered suitable for this kind of treatment. For all oral PUVA protocols, the initial dose should be based on the skin type and can vary from approximately 0.5 and 1 J/cm², with increments of 0.5 J/cm² given for each subsequent treatment or every other treatment until asymptomatic mild erythema is observed in the vitiligo lesion. PUVA is contraindicated in children.\[48]\n
b) **PUVA-sol (Psoralen & Solar exposure)**

PUVA-sol is the use of UVA radiation from sunlight in combination with oral or topical psoralens. The biggest disadvantage of PUVA-sol in comparison with PUVA is the absence of precise UVA dosimetry. PUVA-sol commonly used in countries where sunlight is in abundance and where the facilities for artificial sources of light are often lacking, works on the same principle, except that natural sunlight is used instead of UVA. It was concluded that the combination of PUVA-sol and calcipotriol is most effective and works faster than PUVA alone.\[49]\n
c) **Topical PUVA**

Topical PUVA may be delivered in different forms: as whole-body bath PUVA for widespread disease or as gel, cream, or lotion PUVA for localized vitiligo. Topical PUVA has carried out cautiously to avoid phototoxicity and koebnerization. The preparation, which is usually in solution or cream form, is applied directly to the lesions, which are then exposed to UVA after 20 min, if topical PUVA is correctly performed, perilesional hyperpigmentation can be observed and can represent an obstacle for continuing the treatment.\[50]\n
d) **Khellin + UV**

Khellin is a naturally occurring furanochromone, derived from the seeds of the Ammi visnaga plant. When combined with UVA (khellin plus ultraviolet A; KUVA), khellin is a photosensitizer that forms monoadducts capable of crosslinking with DNA. This
photosensitization stimulates melanocyte proliferation and melanogenesis, similar to psoralen plus UVA (PUVA) in vitro. The commonly reported oral dose of khellin is 100 mg given 2.5 h before UVA irradiation (5–15 J cm⁻²). Topical KUVA also appears to be useful in localized vitiligo and in children. [51]

e) Melagenine
Melagenine (melagenina) is a hydroalcoholic extract of the human placenta that was first identified chemically and used clinically to treat vitiligo in 1986 by Cao et al. in Havana, Cuba. Melagenine contains alpha-lipoprotein, endothelin (ET), adrenocorticotropic hormone (ACTH), glycolipids, sphingolipids and phospholipids. In 1991, Suite and Quamina reported a study in 16 vitiligo patients, whereby five (31%) showed repigmentation when topical melagenine was administered three times daily in combination with infrared radiation, and without any toxic effects. [52,53]

B) Phototherapy
Phototherapy is a longstanding established treatment for vitiligo. Until the mid-1990s, psoralen plus UVA (PUVA) photochemotherapy was the primary UV-based treatment option for vitiligo. In 1997, Westerhof and Nieuweboer-Krobotova first reported the efficacy of narrow-band ultraviolet B (NB-UVB) in vitiligo, and subsequently several studies supported the effectiveness of this modality. [54]

a) Broadband UVA (320-400)
UVA1 phototherapy means the use of long-wavelength (340–400 nm) UVA radiation. A specially developed metal halide source for high UVA intensity, predominantly in the UVA1 range and free of measurable radiation below 320 nm (UVB-free), was first introduced in 1981. The pioneering study examined the efficacy of UVA1 phototherapy in patients with widespread vitiligo. The patients were exposed to low to moderate single doses, between 20 and 50 J cm⁻², three to four times weekly. The length of the courses varied greatly, from four to 35 sessions. A good result was seen in only one out of eight treated patients. [55,56]

b) Broad-band UVB (BB UVB)
Wavelengths from 290 to 320 nm (BB UVB), were widely used in the past for the treatment of a variety of skin disorders. Regimentation results vary among the devices. The 69% of subjects achieved at least 75% re-pigmentation after 30 sessions with another device which
peaks between 311 and 315 nm. The patients showing the best results were those with facial lesions and skin types V and VI.

e) NB UVB
Targeted NB-UVB was first described in the management of vitiligo by Lotti et al. in 1999. The NB-UVB initial dose starts at 150 m J cm\(^{-2}\) and is increased by 10–15% of the previous dose for each visit. For most patients giving treatment NB-UVB, re-pigmentation may be seen within one to two months, but if no response will be seen in three to six months the treatment should be discontinued. Patients were informed that some degree of re-pigmentation should be observed within 30 treatments; weather in some cases initial re-pigmentation may occur as late as after 50 treatments, and it is observed that these late-responders will have excellent re-pigmentation.[57]

d) Targeted phototherapy
By using special delivery systems, such as fiber-optic cables, focused light energy can be directed specifically towards lesional skin. Thus, this has also been termed microtherapy, concentrated phototherapy, and focused phototherapy. In the management of vitiligo, results using five different types of targeted phototherapy have been reported: excimer laser; monochromatic excimer lamp; hand-held multichromatic incoherent UV sources; low-level laser therapy; and photodynamic therapy. Newer phototherapy units capable of emitting light in a more targeted manner and also with higher fluencies, the lesions can be selectively treated while the normal skin is spared.[58,59]

e) Lasers
Helium–neon laser. Low-energy helium–neon (He–Ne) lasers (632.8 nm) have been used in a variety of clinical treatments including vitiligo management. He–Ne laser light was administered locally at 3.0 J/ cm\(^2\) with point stimulation once or twice weekly. A recent study demonstrated that a He–Ne laser induced a growth stimulatory effect on functional melanocytes Excimer laser 308 nm. The excimer laser represents the latest advance in the concept of selective phototherapy. It emits a wavelength of 308 nm and shares the physical properties of lasers: a monochromatic and coherent beam of light, selective treatment of the target and the ability to deliver high fluences.[60,61]
f) Non – Laser light source

Excimer laser/lamp vs. NB UVB, excimer laser vs. /excimer lamp. In the last few years, studies have been published that compare the excimer laser or light with the conventional NB-UVB Phototherapy, Mercury arc lamps.[62]

Different devices equipped with high-pressure mercury arc lamps are now available for targeted phototherapy. Usually, the light is delivered to the skin by means of an optic fiber, Because of the emission spectrum of these lamps, this is also referred to as ‘targeted broad-band UVB.[63]

Both these comparative studies suggest that treatment with the excimer laser or MEL 308 nm may allow regimentation within a shorter period of time than NB UVB phototherapy does, while limiting exposure to only selected areas. The results showed that the 308 nm excimer lamp and laser showed a similar efficacy in treating vitiligo.[64,65]

8) Additional therapies

a) Skin camouflage

Self-tanners in gel, cream, lotion, or spray give the skin a brown colour that resembles a natural tan, and normally lasts 3–5 days. Instant colour self-tanners, available by some manufacturers, thanks to a colour guide, give a tanned colour instantly. The active ingredient is DHA, a sugar that reacts with the proteins of the stratum corneum, and gives a tan resembling the solar UV-induced tan. This is due to the so-called Maillard’s reaction, after the author who studied the chemical reaction that golden the crust of bread in the oven. Traces of metals such as iron, titanium, zinc, or alpha-hydroxy-acids such as lactic acid can inactivate the product. They can be used throughout the year, they are waterproof.[66,67,68]

b) Depigmentation

The depigmenting approach is quite recent, deriving from the observation of unwanted depigmenting action of the phenol derivatives. The first suggested target was the enzyme tyrosinase, and the capability of different phenol derivatives to act as alternative substrate of the enzyme or as competitive inhibitor was evaluated. Structural studies have indicated the role of the position and of the type of substitutes in the phenolic ring to allow the compound to be hydroxylated or oxidated by tyrosinase.

HQ acts as alternative substrate, according to most part of phenol/catechol compounds, because it is similar to tyrosine. HQ can be thus oxidized by the enzyme without generating the pigment. In addition, the produced quinones are able to react with the sulphhydryl residues of the proteins generating oxidative damage and affecting the cell growth.\textsuperscript{[69,70]}

c) Cosmetic
Many different kinds of concealers are available, both over-the-counter and through a dermatologist. Remedial cosmetic cover creams help conceal the blemish of vitiligo at least temporarily. Ask your doctor for recommendations and try different brands until you find the one that works best for you. A high concentration of pigment is incorporated into water–free or anhydrous foundations to give a color that matches the patient's skin, thereby concealing vitiligo patches.\textsuperscript{[71,72,73]}

d) Sunscreen
Sunscreen act by one of the two mechanisms, either by absorbing UV rays or by blocking or/and scattering these rays. Chemical sunscreens function by absorbing UVB and/or UVA. Nowadays, protection against both UVA and UVB is very common and as a result, to prevent sun induced darkening of the surrounding normal skin, broad spectrum high protection factor sunscreens (SPF15-30) which provide protection from UVB and UVA light should be used. sunscreens often contain a mixture of light absorbing chemicals. Sunscreen’s efficacy in absorbing UVB is measured by the sun-protective factor (SPF). In patients with darker skin types (>III), we usually recommend the use of two different sunscreens: the one on the vitiliginous lesions with SPF around 15 and another one with SPF 50+ on surrounding healthy skin, if possible with a high UVA protection factor.\textsuperscript{[74,75,76]}

e) Topical treatment
In adults with recent onset of vitiligo, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Skin atrophy has been a common side effect (B/1+). Topical pimecrolimus should be considered as an alternative to a topical steroid, based on one study. Depigmentation with \p-(benzyloxy) phenol (monobenzyl ether of hydroquinone) should be reserved for adults severely affected by vitiligo (e.g., more than 50% depigmentation or extensive depigmentation on the face or hands).\textsuperscript{[77,78]}
f) Drug affecting immune system

Oral Corticosteroids- Corticosteroids have broad-spectrum immunosuppressive activity. Low-dose oral prednisolone (0.3 mg kg⁻¹ for 2 months, half of the initial dose for 3rd month and again halved for 4th and 5th months) led to stability and regimentation in 87.7% and 70.4% of 81 active vitiligo patients, respectively, with minimal side effect.⁷９

Zinc - Topical steroid application with or without supplementation of oral zinc sulphate 440 mg per day were given. Notably, 13.3% of the patients receiving zinc developed gastrointestinal side effects.⁸⁰

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