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A COMPREHENSIVE REVIEW ON CURRENT TREATMENTS OF VITILIGO

Minhaj Sohail Shakil Patel[1]* and Ifra Shazmeen[2]

[1]Dept. of Medicinal Chemistry, NIPER-Hyderabad.

[2]Dept. of Pharmaceutics, YB Chavan College of Pharmacy.

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***Corresponding Author**
Minhaj Sohail Shakil Patel
Dept. of Medicinal Chemistry, NIPER-Hyderabad.

ABSTRACT

Vitiligo a long-term pigmentary disorder with unknown origin affecting about 0.5-1% of worldwide population characterized by depigmentation of skin, hair and mucus membrane resulting from destruction or reduction in the number of melanocytes. Two types are classified in vitiligo namely segmental and non-segmental vitiligo. This disorder shows dreadful impact on the psychology, confidence and self-esteem. This review covers about the diagnosis, symptoms, types, management and treatment of vitiligo. The treatment strategies aim to control the spread of disease in order to limit the area involved by de-pigmentation and further re-pigmentation of the affected area by suppressing the immune response or by surgical intervention.

KEYWORDS: Vitiligo, Types of Vitiligo, Diagnosis, Signs & Symptoms, Treatment.

INTRODUCTION

Vitiligo is a skin disorder[1] that results in the formation of depigmented patches[2,3] or hypopigmented macules due to selective destruction[2] or reduction of melanocytes[4] the cells that produce pigment in our skin.[1] Vitiligo affects 0.1-2% of the World's population.[5]people of all skin types and all ages can be affected.[1] In most of the cases, white patches develop or expand slowly overtime, and in some cases it never progress and remains stable.[1] Vitiligo can be segmental or non-segmental depending upon the morphology of the clinical involvement. It can also be classified as stable or unstable based on the activity of disease.[2] Many theories have been put forward to explain the pathogenesis of vitiligo and mechanisms that leads to the loss of functional melanocytes from the epidermis. The important ones include a genetic predisposition, autoimmune destruction of

melanocytes, altered redox status and free radical mediated melanocyte damage, heightened sympathetic response and catecholamines/neurotransmitter mediated melanocyte damage, and impaired melanocyte adhesion or melanocytorrhagy.[2] Mode of therapy is based on decreasing the activity, thereby achieving stability and later inducing pigmentation.[6]

TYPES OF VITILIGO

Table 1: Types of Vitiligo.

Segmental	Non-segmental	Unclassified
Uni-segmental	Acrofacial	Focal
Bi-segmental	Generalized	Mucosal
Multi-segmental	Generalized with halo naevi	
	Universal	
	Mixed	

Vitiligo is classified into Segmental Vitiligo, Non-Segmental Vitiligo and Unclassified according to *Vitiligo Global Issues Consensus Conference*.[7] Segmental vitiligo lesions (Fig.1) are characterized by generally one and less commonly two or multiple segments. Most common form is Uni-segmental form which consists of one or more macules particularly on one side of the body with the involvement of body hair with early age of onset, and rapid stabilization while non-segmental vitiligo lesions are distributed bilaterally in an acrofacial pattern (i.e. affecting the face, hands or feet) or scattered symmetrically over the entire body.[8]

Non-segmental vitiligo (NVS) comprises of acrofacial, generalized, universal, mixed forms. NVS can initially have an acrofacial distribution, which can later progress to the generalized or universal form. Acrofacial vitiligo (Fig. 2) can affect face, hands, feet and generally involve the perioral region and tips of the fingers. In a study of latent class analyses, two types of non-segmental vitiligo have been identified; the first is of early onset (i.e. before the 12 years of age) and generally associated with halo naevus (Fig. 5) with premature greying of hair, while second type is of late onset and is mostly associated with an acrofacial pattern. In generalized vitiligo (Fig. 4), patient had a few acrofacial lesions for 10 years that evolved within 6 months into generalized form, spreading to the trunk. Universal Vitiligo (Fig. 3) affects about 80-90% of body surface area and is the most common form of vitiligo. Generalized vitiligo usually precedes Universal vitiligo. Mixed vitiligo is defined as the combined involvement of both segmental and non-segmental vitiligo in one patient. Generally segmental vitiligo precedes the non-segmental vitiligo. Rare class is also

considered as Unclassified type and consists of Follicular Vitiligo, Vitiligo Punctata and Vitiligo Minor. Vitiligo minor is likely to be limited to dark skinned individuals. The term minor here refers to incomplete pigmentation with pale skin compared with healthy skin.[8,10]

The presence of focal lesions (i.e. small isolated white macule) with no segmental distribution that have not evolved into non-segmental or segmental vitiligo after 1–2 years but can evolve to segmental vitiligo or non-segmental vitiligo is regarded as unclassifiable vitiligo.[8,10]

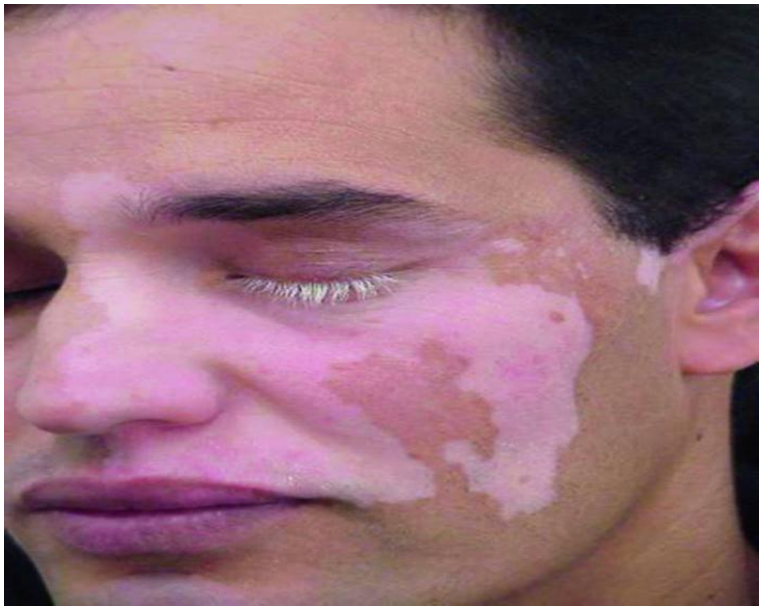

Fig. 1: Segmental Vitiligo.

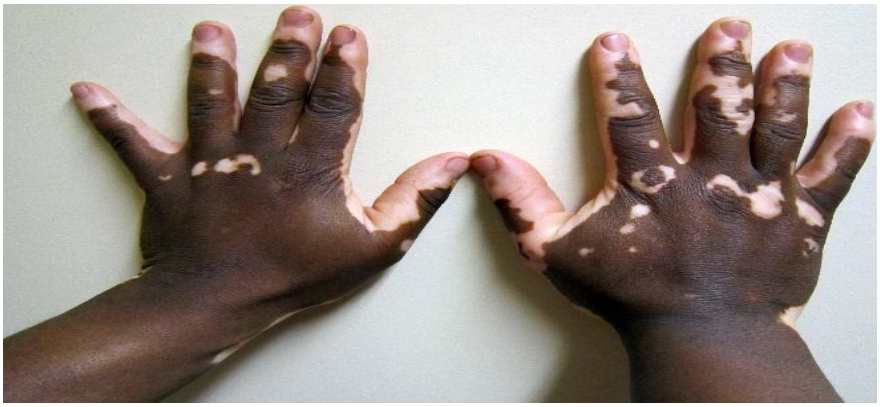

Fig. 2: Acrofacial Vitiligo.

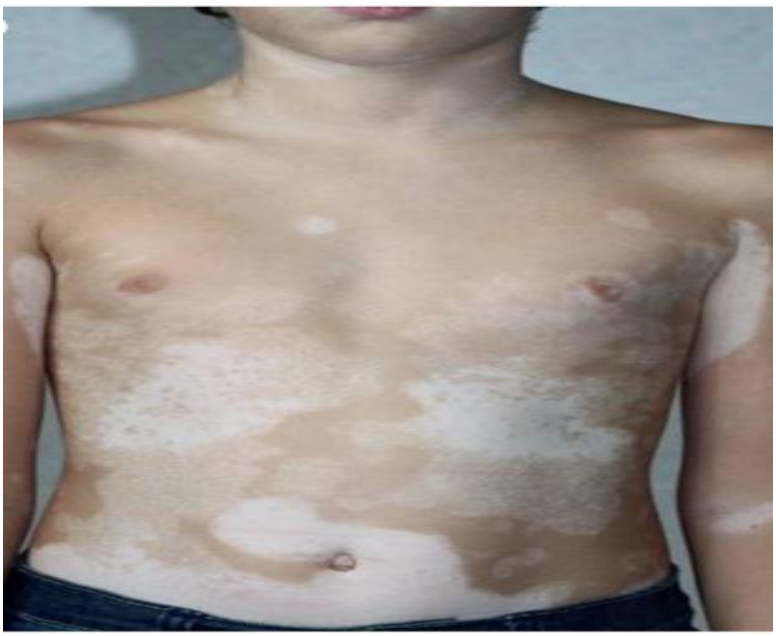

Figure 3: Universal Vitiligo.

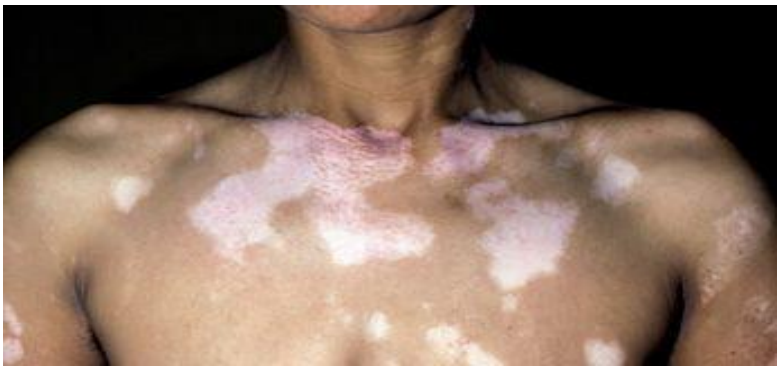

Figure 4: Generalized Vitiligo.

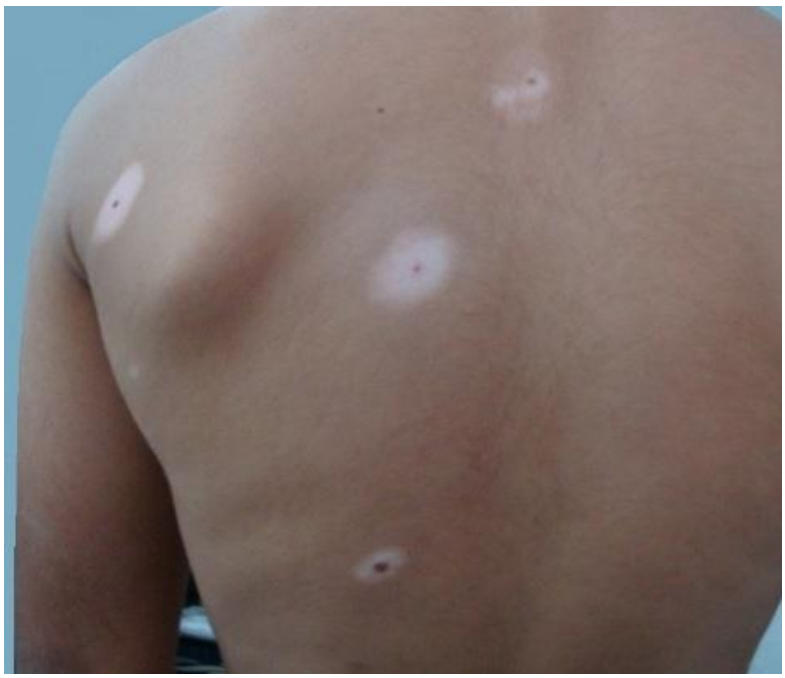

Figure 5: Generalized Vitiligo with halo naevi.

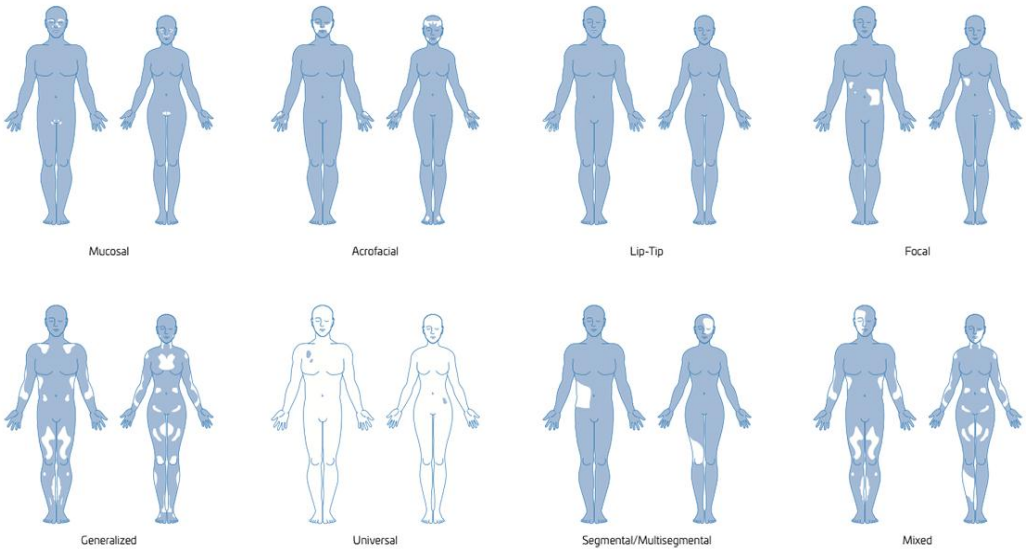

Fig. 6: Different patterns of Vitiligo.

DIAGNOSIS CRITERIA

Diagnosis is based on careful site examination of acquired, white lesions on the skin with no associated inflammation.[11] During early phases ultraviolet light can be used for detection.[12,13] Evaluation might also include a skin biopsy and blood tests.

DIFFERENTIAL DIAGNOSIS

There are other conditions that make the skin change or lose its pigmentation. Differential diagnosis is made versus.

1. **Piebaldism;** This is a rare depigmentation disorder due to a mutation of c-kit migration of melanocytes. It is characterized by stable and circumscribed white patches present at birth, affecting the face, sternal and abdominal zones, knees and elbows.
2. **Achromic nevus:** This is a well-limited depigmented area, stable and evident at birth, in which melanocytes are either normal or reduced.
3. **Post-inflammatory leukoderma:** The condition in which patients have a history of pre-existing dermatosis.
4. **Pytiriasis alba:** This condition starts off with red and scaly areas of skin,which fades into scaly lighter patches of skin.
5. **Depigmented lesions in leprosy:** The condition which shows anesthetic disturbance of sensibility.
6. **Albinism:** It is a genetic disorder that causes the skin, hair, eyes to have little or no color.[11]

SIGNS AND SYMPTOMS

Symptoms includes depigmentation and occurrence of noticeable, prominent, pale patchy areas on skin which are non-contagious[1] and can cause itching [14] and may expand in size.[14,15] Other less common signs may include:

- Premature whitening or graying of the hairs on scalp, eyelashes, eyebrows or beard. [16,17]
- Loss of color in the tissues that line the inside of the mouth (mucous membrane).[18]

MANAGEMENT

- Management includes avoiding direct exposure to sunlight and tanning of the skin.[1]
- Use of topical sunscreen with SPF50 or more.[1]
- Skin Camouflage in mild cases can be done by using make-up or self-tanning compounds to make the patches less noticeable.[1,19]
- Medical and surgical re-pigmentation therapies can be carried out.[19]

CAUSES

The onset of Vitiligo can be instigated by various triggers including changes in immune system, genetics, sunburn,[20] exposure to phenolic chemicals, association with other autoimmune disorder; however trigger is unknown in most of the cases.[1] These type of triggers are all thought to induce oxidiative stress in the melanocytes.[21]

Genetics: Vitiligo is a multifactorial disease with genetic susceptibility. Although Vitiligo affects approximately 0.1-2% of the general population[5] the risk of patient sibling developing disease is 6% and for identical twin is 23%. [17]

Oxidative stress: Accumulating evidence suggests that melanocytes from vitiligo patients have intrinsic defects that reduce their capacity to manage cellular stress.[22] Epidermal cells, including melanocytes, are constantly exposed to environmental stressors, such as ultraviolet (radiation and various chemicals, which can increase production of reactive oxygen species.[23] Although healthy melanocytes are capable of mitigating these stressors, melanocytes from vitiligo patients seem more vulnerable.[17]

Environment: Multiple studies suggest that exposure to specific environment factors may play a central role in disease onset. Later studies confirmed that a history of exposure to phenolic and catecholic chemicals found in dyes, resin/adhesives etc. [17]

Autoimmune associations: Vitiligo is sometimes associated with autoimmune and inflammatory disease such as Addison's disease, alopecia aerate, scleroderma, psoriasis, pernicious anemia and celiac disease.[18]

Immunity: Immune system mistakenly attacks and destroys the melanocytes of the skin causing autoimmune destruction of melanocytes.[2]

TREATMENTS OF VITILIGO

1. Pharmacological treatment

The pharmacological treatment also known as pharmacotherapy or drug therapy includes the use of Corticosteroids and Calcineurin inhibitors which helps to suppress or decrease the immune response activity because in Vitiligo the body's immune cells kills the melanocytes which in turn decreases the production of melanin and causes depigmentation.

Corticosteroids therapy

Creams containing corticosteroids can be effective in returning the pigmentation. The topical corticosteroid therapy is regarded as the first line therapy for Vitiligo. But these corticosteroids cream can cause breakdown and thinning of the skin or can cause the stretch marks, telangiectasias and they are likely to cause systemic side effects so they must be used under dermatologist's care. Thus, the employment of high-power topical corticosteroids is more effective to treat localized areas, being more suitable on the face, elbows and knees, although some authors prefer the use of low-power corticosteroids on the face and flexural areas.[8,10] In a group of 101 children, a study compared the use of high and moderate power topical corticosteroids, in both groups, 64% of cases showed re-pigmentation, 24% of cases showed stabilization and 11% of cases showed worsening of condition.[24] The studies have recommended that the high-power topical corticosteroids for treatment of localized vitiligo should not be used more than 2-4 months and instead low-power corticosteroids or use of other immune-suppressants must be considered so as to reduce the risk of side effects and if no clinical response is seen with corticosteroids in 3-4 months, then they should not be used.[25]

Calcineurin inhibitors therapy

Calcineurin inhibitors includes cyclosporin, tacrolimus and pimecrolimus which are in the class of Immunosuppressive agents and are generally used in the patients who undergone organ transplantation as well as in auto-immune disorders so as to suppress the immune

response. Tacrolimus and pimercolimus are used for the topical treatment for vitiligo while calcineurin is of no use because it lacks the cutaneous absorption. Cyclosporin, Tacrolimus and Pimecrolimus inhibits the calcineurin and thereby inhibiting the activation and maturation of T-cells. The cyclosporin binds to cyclophilin while tacrolimus and pimecrolimus binds to FK 506 binding protein (FKBP) also known as macrophilin-12. These complexes then attach to calcineurin (a Ca^{+2}/calmodulin dependent protein phosphatase). The calcineurin dephosphorylates the NFAT (Nuclear factor of activated T-cells). The dephosphorylated NAFT then gets translocated from cytoplasm to the nucleus and complexes with nuclear components required for complete T-cell activation, including transactivation of IL-2 and other lymphokine genes. But binding of Calcineurin inhibitors to calcineurin inhibits the dephosphorylation of NFAT and so NFAT does not enter the nucleus and so the gene transcription is prevented. Tacrolimus inhibits the gene transcription for IL-3 IL-4, IL-5, TNF-α and INF-γ. In addition to IL-2, pimecrolimus also inhibits the production of IL-4, IL-5, IL-10, TNF-α and INF-γ.[26]

Combination therapy

The combination therapy includes the use of Calcipotriol and topical corticoids like betamethasone dipropionate. This combination therapy is used in the patients who are resistant to previous treatments like tacrolimus and topical corticoids with 75% of re-pigmentation rate observed in a series of cases.[8]

2. Phototherapy

The physical treatment includes the treatment with UV radiation both with UV-A and UV-B. The mechanism of action is fully not understood but it has been reported that the UV radiation shows immune-suppression and inhibit melanocyte destruction.

Narrow band UV-B (NBUVB) treatment

The NBUVB radiation ranges from 310-315nm and is considered as a gold standard for the treatment of diffuse vitiligo. The use of NB UVB (311 nm) phototherapy in comparison with topical PUVA for vitiligo was first reported by Westerhof and Nieuweboer-Krobotova in 1997. In their study two patient groups were investigated with extensive generalized vitiligo with 3 months of duration. The first group was treated for 4 months while second group was treated twice weekly with a follow up of 3, 9 and 12 months. Their study reported that 67% of patients undergoing NB UVB phototherapy developed re-pigmentation compared with 46% of patients receiving topical PUVA after 4 months of therapy. After 3 months of

therapy, 8% of patients in the second group showed more than 75% of re-pigmentation in comparison with 63% after 12 months. They also reported that the face showed good re-pigmentation while the extremities responded poorly with lower adverse effects compared with PUVA.[27]

In a double-blind randomized study, it was reported that 64% of patients showed 50% re-pigmentation with the use of NBUVB in comparison to 36% re-pigmentation in the group treated with systemic PUVA.[8]

PUVA (Psoralen + UV) treatment

PUVA is a type of photochemotherapy in which Psoralen is given in the forms of 8-methoxypsoralen, 5-methoxypsoralen or trimethylpsoralen orally or topically along with the administration of UV-A. Psoralen are naturally occurring organic compounds in the class of furanocoumarins obtained from seeds of Psoralea corylifolia. The Psoralen acts as a photosensitizing drug and absorbs the UV light and itself acts as UV light and therefore enhances the activity of the light.

For treatment of vitiligo, the UVA is irradiated twice a week with 24-48 hours interval between the two irradiations. Only extensive vitiligo patients are considered for this treatment. Generally, 8-methoxypsralen was prescribed with a dose of 0.6 mg/kg two hours prior to the irradiation. The intake of food, especially fatty foods play a role in achieving the peak blood levels of all psoralen preparations. The peak blood levels of psoralen preparations widely vary from patient to patient. About 50 to 300 treatments are required. The dark-skinned individuals showed maximum response to PUVA and re-pigmented areas can remain stable during decades, but if therapy is stopped, partial re-pigmentation may reverse. Children are contraindicated with use of PUVA therapy.[28]

3. Melanocyte transfer

The patients who are unresponsive to other therapies are recommended for surgical melanocyte transfer. The surgical melanocyte transfer technique is based on the principle that to transplantation of autologous melanocytes from normal pigmented donor skin to the depigmented skin of recipient. Many surgical techniques are available for the surgical transplantation of melanocytes which includes miniature punch grafting, suction blister grafting, transfer of non-cultured epidermal suspension, and transfer of cultured melanocytes. Culturing techniques are very time consuming as it requires culturing of the cells for weeks

and it also requires skilled highly trained personnel and well-equipped laboratories and hence the cost of whole technique is more.

The vitiligo was categorized according to extent of stability and severity. The area of the macules was calculated based on the radius of the circular macules in cm scale. The large sized irregular macules are calculated by dividing the lesions into geometrical shapes and then determining the area. According to a study carried out by use of non-cultured melanocyte transfer for treatment of stable vitiligo in total 51 patients, it was observed that out of total number of patients, 18% of patients got poor re-pigmentation, 10% of patients got fair re-pigmentation while 62% of patients got good re-pigmentation. It was also observed that the patches over lips, legs, face and trunk got good response while patches over bony prominences got poor response.[6]

CONCLUSION

Vitiligo is not usually harmful medically and causes no physical pain, its emotional and physiological effects can be devastating. Counseling of patients can be done to avoid some therapies of dubious efficacy is a major step. Although there is no cure for Vitiligo but the current treatments help in preventing recurrence and checking its further progression. While agents that address immune suppression have been demonstrated to provide benefit to patients. Combination therapy shows promising results. Surgical management with autologous non-cultured melanocytes transfer technique remains a good option for the patients having stable Vitiligo.

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