

Various Treatments for Vitiligo: Problems Associated and Solutions

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ABSTRACT

The present review includes the study of vitiligo, its different types and treatments available into the market. Vitiligo is a skin disorder in which white patches occurs on the skin may be in the form of lesions or on the whole body. These white patches occur due to destruction of colour producing cells melanocytes. Different drugs like methoxsalen, trioxsalen and psoralen are available for the treatment of vitiligo in oral capsule form or topical cream or lotion form. Psoralen with light therapy is also given which is also known as PUVA therapy. Treatment of vitiligo always poses a problem as the patient compliance is less. Most of the times the treatment gets discontinued by the patients as the effect are very slow. This inefficiency leads to frustration in patients. This may be one of the reasons for discontinuation or 'give up' by the patients. Some patients also face the problem of additional symptoms or side effect like itching, burning, gastric disturbances etc. This review discusses on all above mentioned issues with problems associated with treatment and the related possible solutions.

INTRODUCTION

Melanocytes synthesize melanin from the amino acid tyrosine in the presence of an enzyme called a melanosome. For the production of skin colour melanin is the necessary pigment. Vitiligo is a skin disorder in which the partial or complete loss of melanocytes from patches of skin produces irregular white spots which are shown in figure 1 (a) & (b). Vitiligo generally affects about 1% of the world population. It does not include racial, sexual or regional differences among the population. Some reports suggest that incidence of Vitiligo in India, Egypt and Japan is higher. It ranges from 1.25% to 6% of the population. Onset of Vitiligo is usually more in childhood or in young adults (20–30 years of age) and in about 30 % there is a positive family history (Gerard and Bryan, 2006). There are three Major Types of Vitiligo: Segmental (SV), Non-segmental (NSV), and Mixed Vitiligo (MV). Segmental Vitiligo starts and stays on one side of the body. It is rarely associated with autoimmune disease. Non-segmental Vitiligo includes all types except Segmental. It is an autoimmune disease and often mirrors on both sides of the body. Mixed Vitiligo overlap of both types in the infrequent cases where Segmental becomes Nonsegmental.

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Clinical lesions are asymptomatic and their size varies from few to many centimetres. Vitiligo often involves white patches on the hands and wrists, feet, arms, face, lips, axillae and perioral, periorbital and anogenital skin. Vitiligo can also affect the mucous membranes of the body such as the tissue inside the mouth and nose. It can also affect the eye (U.S. Department of Health and Human Services, 2010). Childhood vitiligo is different from the adults. It shows higher incidence in females. Adequate treatment of the childhood vitiligo is very essential because it cause marked psychosocial and long lasting effect on the self-esteem of the affected children and the parents (Kanwar and Kumaran, 2012). In general vitiligo the white patches do not spread. But in some cases the white patches will spread to other areas of the body. In some people patches spread slowly while in some people quickly. In case of higher physical or chemical stress white patches spread rapidly. Due to physical or emotional stress white patches spread more rapidly. On histologic examination, Vitiligo usually appears indistinguishable from normal skin. However it is characterised by loss of melanocytes, as revealed by electron microscopy, it also may be diagnosed by immune histochemistry for melanocyte associated proteins. The pathogenesis of Vitiligo is multifactorial. It includes three main factors: genetic, immunological, and environmental. Clinically, environmental factors play important role in the development of Vitiligo.

Trauma, eczema, chemical agents, and fragility of keratinocytes are major causes Vitiligo. So these factors should also be taken into account during the treatment (Jimi *et al.*, 2011). Theories of Pathogenesis of Vitiligo include Autoimmunity, Neurohumoral factors toxic to melanocyte and released by nearby nerve endings, Self destruction of melanocyte by toxic intermediates of melanin synthesis. Skin lesions are frequently localized to the seborrheic area in stress induced vitiligo. The lesions are localized to sites of injury or pressure in case of traumatic vitiligo. Depigmented lesions tend to occur in areas of a specific pre-existing dermatitis and it is called dermatitis associated Vitiligo (Vinay *et al.*, 2007).



Fig. 1: 1(a) and 1(b).

DIAGNOSIS OF VITILIGO

Differential diagnosis of vitiligo is very difficult. To diagnose the exact vitiligo one should be able to differentiate between different conditions of the skin like complete depigmentation, hypo pigmentation and normal colour of the skin. Diagnosis of vitiligo is very difficult in patients having light complexion of the skin colour. Wood's light is very useful to diagnose the vitiligo in the patients having skin type I and II. Pure tone and speech audiometer, Sound treated room, Cochlear Emission Analyzer Madsen, Immittance meter, Evoked Response Audiometer Nickolet Compact four, Wood's light lamp equipments can be used for the diagnosis of vitiligo (Talia, 2009).

TREATMENT OF VITILIGO

Etiology of the Vitiligo is still unknown. But it involves some theories like Auto immunity, cytotoxicity, triggering, neural, free radicals and genetic. It can be treated by oral or topical formulations of the drug alone in mild cases but in severe case of Vitiligo Light therapy is also given with the consumption of medication to increase the pigmentation of the skin. The treatment of leukoderma or Vitiligo requires not only a deposition of pigment in the areas of depigmentation, but it also requires a redistribution of pigment from hyper pigmented borders, so that the result will be an even distribution of the normal amount of cutaneous colouring. It also depends on the presence of the type of the cell. Possibility of formation of melanocyte in inter-follicular epidermis is decreased by the presence of keratinocyte stem cells in the similar location (Rafael, 2009).

Treatment of vitiligo with herbal medicines

From the list of Chinese herbs acting for the treatment of vitiligo decoction of xiaobailing changyee powder and three

yellow powders are most effective. These medicines include xanthumstramanum, sophoraflavescens, atractylodes japonica, arisaemaamurensis. Some other herbs include carthamustinctorius, eclipta prostrate, pleuroptereesmultiflorees, salvia miltiorrhiza, sesamumindicum, spatholobussuberectus, rehmaniaglutinosa. Applying these medicines onto skin improves skin coloration and treats the vitiligo. Indian herbs include cassia accidentalis, eclipta prostrate, curcuma longa, picrorrhizakurroa, psoraleacorylifolia, tribulusterrestris. In this mainly photosensitizers and blood purifiers are used. Photosensitizing agents include psoraleacorylifolia, semicarpusanacardium and ficushispida. They are administered locally as well as systemically with the sun exposure. Blood purifiers include curcuma longa, ecliptaAlba, tinosporacardifolia, hemiclascusindicus, acasia catechu and acaranthusaspara. Exact mechanism of the herbs is unclear but it involves some mechanisms like phototoxic reactions, melanocyte proliferation, promoting anti-inflammatory activity and trigger reduction (Jimi *et al.*, 2011).

Traditional Treatment

Red clays found by the river side or on hill slopes can also be used for the treatment of vitiligo. It can be given by mixing with ginger juice. Copper in the clay brings skin pigmentation back and ginger facilitates increased blood flow to the spot which helps into the repigmentation of the spots. Radish seeds powdered with the vinegar and paste is formed. This paste can be applied to treat the vitiligo. Mixture of turmeric and mustard oil which is prepared by heating two of them is also helpful in the treatment of white patches (Priyanka *et al.*, 2010).

Yoga therapy

Kapalbhati is helpful in the treatment of vitiligo. Because of inhalation and exhalation kapalbhati provides aeration to blood and purifies blood circulation. This is beneficial in different skin diseases like vitiligo, psoriasis and other allergies (Priyanka *et al.*, 2010).

Homeopathic treatment

Homeopathy is an alternative medicine originated in Germany in 18th century and it is adapted by many countries. Ars.ach, Bacillinum, Graphites, Mercasol, Nat mur, nuxvom, sil, sulph, thuja etc. medicines can be used under homeopathic treatment (Priyanka *et al.*, 2010).

Ayurvedic treatments

In Ayurveda vitiligo is known as Switra and it is mainly caused due to the Pitta Dosha as aggravated Pitta leads to accumulation of toxins (ama) in deep layers of the skin which leads to the condition of Vitiligo. Basic treatment of this disease includes Calming imbalanced body energies, cleansing blood and administering the herbs which restore the skin colour. Poor digestion cause build-up of toxins into the body thus it is a root cause for the disease. Therefore, restoring digestion is the essential part of the body (Jiva Ayurveda). Generally Ayurvedic treatment

of Vitiligo involves four steps. First step is Purification therapies (Shodhana Karma), which includes use of herbal decoction of Psoralea Corylifolia and Eurphorbianerifolia. Second step includes Oil massage, in which oil is selected on the basis of disease state (roga) and Patient Examination (rogiPariksa). Third step is exposure of lesions to the sun rays depending on the tolerance of the patient (Sooryapadasanthapam). And fourth and last step is delivery of decoction (kwatha) made of Ficushispida (malayu), Pterocarpusmarsupium (asana), Calllicarpamacrophylla (priyangu), Peusedanumgraveolens (satapuspa), Coleus vettiveroides (ambhasa), and alkaline extract of Buteamonosperma (palasaksara), along with an alcoholic preparation of jaggery (the preparation is called phanitha in Ayurveda) to the patient. The diet should be salt-free and should contain buttermilk during the treatment of decoction (Saravu *et al.*, 2010). Different ayurvedic formulations of herbs which are available are given in the table 1.

Table. 1: different Ayurvedic Formulations of Herbs.

Type of Ayurvedic Formulation	Probable herbs used
Lepa (Topical preparation)	Ankollakadi, Avalgujadi, Bakucyadi, Balyadi, Bhallatakadi, Bhringarajadi, Gandhakadi, Grhadhumadi, Gunjadi, Gunjaphaladi, Katukalabvadi, Manasiladi, Maricadi, PancaNimbava, Pathyadi, Patrakadi, Putikadi, Talakadi, Triphaladi, and Vayasyadi
Kashaya (Mixtures)	Bakucibeeja yoga, Bakuciprayoga, Bhadrodumbarikadi yoga, Dhatryadikwata, Kakodumbarikakasayaand Khadiradikashaya
Churna (Compound Powder)	Bakucyadyachurna, Kakodumbarikadi yoga, Khadirasaradichurna and Pancanimbachurna
Ghrita (Paste)	Dantyadi ghrita, Mahamarkaraghrita, Mahaneelaghrita, Mahatiktakaghrita, Mahavajrakaghrita, Neelakaghrita, Neelighrita, Neelinyadi ghrita, Somarajighritaand Tiktakaghrita
Avaleha (Oral Semisolid preparations)	Bhallatakavalehaand Vidangadileha
Thaila (Oil preparations)	Aragwadhayadyathaila, Citrakadyathaila, Jyotismatithaila, KustaKalanalathaila, Kustarakasathaila, Laghumaricadyathaila, MahaVajrakathaila, Manasiladyathaila, Maricadyathailaand Vishathaila
Asava Arista (Fermented preparations)	Kanakabindvarista and Madhwasava
Vati/Gutika (tablets)	SwayambhuvaGuggulu, ThriphaladigutikaandBrhatSwayambhuva Guggulu
Rasousadha (Formulations containing processed minerals and metallic salts)	Candraprabhavati, Galitakustari rasa, Khageswara rasa, Kustebhakesari rasa, Medanisara rasa, Pittalarasayana, Talakeshwara rasaand Vijayeswara rasa

Topical allopathic treatments

It involves different topical formulations of steroids and immunomodulators. Steroids applied topically are helpful to treat the patches of vitiligo. Potent corticosteroids like betamethasone, valerate, triaminolone and very potent corticosteroids like alobetasol, fluticasone propionate are helpful to obtain marked or

almost complete repigmentation of the skin. Immunomodulators like tacrolimus and pimecrolimus are helpful in the treatment of vitiligo when applied topically. These can also be used to treat the small and difficult areas like eyelids (Priyanka *et al.*, 2010; Navneet *et al.*, 2012).

Surgical therapies

In surgical therapies white patches are treated with the help of different surgeries. It involves different mechanisms of surgery. In Autologous Skin Grafts technique grafts are implanted into perforations prepared at the recipient sites. Patients with segmental vitiligo are best candidate for this type of grafting. In blister grafting blisters are used. These blisters can be induced by different ways such as vacuum or liquid nitrogen. At the dermoepidermal 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. To overcome these limitations epidermal cell transplantation can be done. This technique involves application of a melanocyte-rich suspension to the affected area and then it is allowed to graft. Only one time treatment is necessary is the main advantage to this technique. Micro pigmentation (Tattooing) technique involves permanent dermal micro pigmentation. It is done by using a non-allergic iron oxide pigment. These pigments provide colour to the skin (Priyanka *et al.*, 2010; Navneet *et al.*, 2012).

Other alternative treatments

If no treatment works for the treatment than alternative cover-ups can be used. Leukodermic skin easily gets damaged to the sunburn and the effect lasts for very long time. So to avoid the excess exposure to the sunlight and prevent the sunburn sunscreens can be used. To hide the untreated white patches onto the skin cosmetics cover-ups are very useful (Priyanka *et al.*, 2010; Navneet *et al.*, 2012).

Depigmentation

It is a drastic form of treatment for vitiligo. It involves fading the rest of the skin of the body so the whole body appears in white colour. For that permanent melanocytotoxic agents like monobenzyl ester of hydroquinone cream and 4-methoxyphenol can be used. (Navneet *et al.*, 2012)

Other Drugs used for the treatment

Trioxsalen is given orally. By increasing skin pigmentation, it increases the tolerance of the skin to UV light. This drug sometimes causes cutaneous reaction. Methoxsalen can be given orally as well as topically. In oral dosage form 20mg/day drug is given 2-4 hours before UV exposure. It causes gastric discomfort. In topical dosage form 0.1% to 1% lotion is applied and sun light or UV light exposure is given. It may cause Acute, Vesicular, Cutaneous photosensitivity reaction. Both the formulation of this drug may cause severe sunburn (Satoskar *et al.*, 1969).

Photo chemotherapy

Application of photochemical reaction is an advantageous for the treatment of vitiligo. Photochemotherapy is Traditional therapy for Vitiligo. This therapy is based on ancient Atharva Veda observations. Psoralen is having very good photochemical response to ultraviolet B as well as ultraviolet A. Because of this reason the treatment includes topical/oral psoralen treatment, followed by exposure to ultraviolet light or Sunlight. This combined treatment is known as PUVA therapy (Psoralen Ultraviolet A therapy). It is based on the observation in Atharva Veda more than 3000 years ago. In this treatment oral psoralen is administered followed by UVA rays exposure. This is FDA approved treatment of Vitiligo and psoriasis. Psoralens are compounds found in many plants. These compounds make the skin temporarily sensitive to UVA. For oral treatment of PUVA, methoxsalen capsules are taken before two hours of the appointment.

There is significant but saturable first-pass elimination in liver, which may cause variations in plasma levels after a standard dose. Methoxsalen has a serum half-life of one hour, but the skin remains photosensitive for 8-12 hours. During this therapy, the patient has to stand in a cabinet containing 24 or more UVA fluorescent bulbs having length of 6 feet. To protect the eyes from the exposure of radiation, the patient should always wear goggles. PUVA promotes melanogenesis in normal skin. Increased pigmentation results from augmented transfer of melanosomes from melanocytes to keratinocytes. PUVA has some side effects like Burning, Itching, Nausea, Tanning and painful erythema. In topical treatment gel or cream of psoralen is applied and then exposure of uv light is given. Dark skin types have better repigmentation than paler skin types. Topical PUVA is an attempt to limit the area that becomes photosensitized (Priyanka *et al.*, 2010; Navneet *et al.*, 2012; Laurence and John, 1941; Bhawna *et al.*, 2012).

MECHANISM OF DRUG PSORALEN

Psoralen is having good photosensitizing characteristics. So it is used in many types of treatments like herbal, alternative, photochemotherapy, topical etc. The exact mechanism of action of psoralen (Methoxsalen) with the epidermal melanocytes and keratinocytes to enhance pigmentation into the body is not known. One biochemical reaction of Psoralen (methoxsalen) is known with DNA. Methoxsalen after conjugation forms covalent bonds with DNA. The conjugation leads to formation of monofunctional and bifunctional adducts. This occurs due to photo activation of the Methoxsalen.

In above reaction Methoxsalen acts as a photosensitizer and cause pigmentation of the skin. Through the blood orally administered methoxsalen reaches to the skin and UVA penetrates well into the skin. The melanocytes present in the hair follicle are stimulated to move up the follicle and to repopulate the epidermis and thus become helpful in the treatment of vitiligo (Laurence and John, 1941).

PROBLEMS RELATED WITH THE TREATMENT

The above treatments are available for the Vitiligo. But these treatments are not that much effective. These treatments are having longer duration of time may be 2 or more than 2 years with continuous therapy. Due to these reasons patients get frustrated and discontinue the treatment. And the penetration of the drug psoralen through skin or absorption through oral administration is also less which lessens the effectiveness of the therapy. Moreover it is having some additional symptoms and side effects also. Drug side effects and additional symptoms include gastric discomfort, cutaneous photosensitivity reaction, Sunburn, Burning, Itching, Nausea, Tanning and painful erythema. Stressful life and other factors like type of clothes smoking habit also affect the treatment negatively.

POSSIBLE SOLUTIONS FOR THE PROBLEMS

In oral treatment the drug first goes into the blood and via blood reaches to the epidermis while in topical treatment the drug direct reaches to the epidermis thus topical treatments are faster than oral treatments. Now in topical preparations permeation of the drug through the skin is difficult. This problem can be solved by adding permeation enhancer to the formulation. Rapid delivery of the drug can be obtained by reducing the particle size of the skin. To obtain small particles novel deliveries of the formulation can be prepared. In Novel deliveries phospholipid-structured vehicles like ethosomes, transferosomes, liposomes, lecithin organogels, lipid emulsions etc can be prepared. Due this novel delivery penetration of the drug can be enhanced through the skin. To treat the additional symptoms additional agents can be given with the treatment incorporating into the same formulation or given separately. For nausea antiemetic agent can be given, for itching and burning soothing agent can be added, for gastric disturbances different antacids like proton pump inhibitors or the agents which reduce the stomach HCl level. Sometimes during treatment inflammation of the skin occurs due to injury to the skin cells. To treat this type of conditions anti-inflammatory agents can be given with the treatment. By changing the living habits of the patients depending on their individual clinical presentation of Vitiligo the disorder can be reduced. Positive thinking and reducing stress could help to reduce the lesions because severe stress increases the lesions. For the patients who are having lesions in a seborrheic distribution adequate rest and consumption of antioxidants is very important. Patients who are having habit to smoke should reduce smoking because it siphons beneficial antioxidants from the body. Tight-fitting shoes or jeans, and elastic stockings should be avoided in case of Vitiligo through friction or trauma.

CONCLUSION

Vitiligo is a skin disorder in which destruction of melanocyte by different means occurs. The above discussed

treatments are available to treat this disorder. Some problems are also there with the treatment so some solutions to those problems are also discussed in above article. But as discussed above due to slow effect and longer duration and also due to some additional symptoms patients get frustrated and discontinue the treatment. This is a major problem with this treatment. So to avoid such things or to resolve this problem patient counselling should be carried out in which patients can be explained about the treatment and they can be taught to keep patience during the treatment to get effective results.

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