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THE INTRICACIES OF VITILIGO WITH REFERENCE TO RECENT UPDATES IN TREATMENT MODALITIES

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ABSTRACT

Vitiligo is a chronic stigmatizing human disease, affecting melanocytes from epidermis basal layer, leading to the development of hypochromic and achromic patches. Its estimated prevalence is 0.1-2% worldwide, regardless of race, gender or ethnic background. The deforming nature of vitiligo causes high psychosocial morbidity. Historically, the cause of vitiligo has been an extensive topic of debate. A wide range of theories have been put forward including genetic, autoimmune, melanocyte growth factors, autocytotoxic and neurogenic mechanisms. The current 'state-of-the-art' thinking is summarised in the convergence theory which suggests that several factors can act synergistically or independently to induce the disappearance of melanocytes from the skin. Because of its complexity, several therapeutic options are available but the quest for an adequate treatment for vitiligo still continues. In this review, we have described the intrinsic and extrinsic factors that regulate human skin pigmentation, focusing on vitiligo and its least known intricacies. This article is dedicated to the introduction of and discussion about the most recent and innovative researches in the treatment of vitiligo.To assist further progress in vitiligo research, an overview on pathogenesis and recent updates on different nonsurgical and surgical treatment modalities are reviewed. It also provides a description of the newly developed techniques that are in the hands of dermatologists, dermato-cosmetologists, and dermatologic surgeons.

KEYWORDS: Vitiligo, Melanocytes, Genetic, Autoimmune, Pathogenesis.

1. INTRODUCTION

Skin pigmentation contributes significantly to the health and quality of life of an individual. Skin imparts color due to the presence of pigment called melanin used to protect the epidermis and the deeper layers of the skin from external aggressions, especially the ultraviolet radiations transmitted by the sun. These pigments are synthesized by specific cells, namely melanocytes, which are located in the deepest layer of the epidermis that is to say, the basal layer of the the epidermis. In the face of the complex mechanisms that regulate human skin pigmentation, any dysfunction or disturbance results in different types of pigmentation defects, which are classified as hypopigmentation or hyperpigmentation and which may occur with or without an altered number of melanocytes.[1-3]

A wide range of disorders can present as cutaneous hypopigmentation. Among them vitiligo is most common depigmenting skin disorder, characterized by acquired, idiopathic, progressive, circumscribed hypomelanosis of the skin and hair, with total absence of pigment cells from the epidermis.[4] However, recent clinical and experimental studies suggest that vitiligo is a result of systemic autoimmune destruction of melanocytes not only in the skin but also in mucous membranes, eyes, hair bulbs and in the ears.[5] This can be more psychologically devastating in people of color due to marked contrast between normal and affected skin. It occurs worldwide, with an incidence rate of 0.1% to 2% without sex predilection.[6-8]

The pathogenesis of vitiligo remains elusive, although many theories such as autoimmune hypothesis, genetics theory, neural hypothesis, autocytotoxic and biochemical, molecular and cellular alterations accounting for loss of functioning melanocytes in vitiligo were elaborated to clarify vitiligo pathogenesis and showed that it was a multifactorial disease involving many different interactions.[9] The understanding of the mechanisms and intricacies of melanogenesis facilitate us to depict the marks observed in vitiligo and allows the development of potential therapeutic strategies.

In the present review, we have explained the intrinsic and extrinsic factors that regulate skin pigmentation, focusing on vitiligo. This article is dedicated to the introduction of and discussion about the most recent and innovative researches in the treatment of vitiligo. It also provides a description of the newly developed techniques that are in the hands of dermatologists, dermato-cosmetologists, and dermatologic surgeons.

2. MELANOCYTES AND PIGMENTATION

Due to the fact vitiligo is a skin disorder, a brief evaluation of the structure and physiology of skin is covered. Human skin is made up of two predominant layers: the epidermis, a stratified squamous epithelium mainly consisting of keratinocytes, and the dermis, an underlying layer of vascularized connective tissue. The epidermis is composed of four cell types: keratinocytes, melanocytes, and two types of non-pigmented granular dendrocytes, Langerhans cells, and Granstein cells.[10]

Melanocytes are highly dendritic cells that contact all keratinocytes; they reside in the basal layer of the epidermis and produce skin pigment called melanin. Melanin is produced in membrane-bound granules called melanosomes. Melanosomes migrate from the center of the melanocyte cell body to the end of the dendrites and are deposited into keratinocytes.[11, 12] The melanosomes accumulate in the keratinocytes and form a shield of melanin, which provides the skin with protection against ultraviolet radiation from sunlight.[10, 13, 14]

The production of melanin is a highly complex process involving many enzymes (mainly tyrosinase, tyrosinase, tyrosinase-related protein 1 (TRP1), and tyrosinase-related protein 2 (TRP2) and cofactors including alpha-melanocyte stimulating hormone (α-MSH), microphthalmia-associated transcription factor (MITF), cyclic AMP (cAMP) elevating agents and UVB-radiation. Melanin plays an important role in the prevention of sun induced skin injury, and is a major determinant of skin color.[15, 16]

All humans have relatively the same quantity of melanocytes, so different skin pigmentations are accounted by variations in melanocyte activity or the rapidity of melanin breakdown in keratinocytes. The hypopigmented lesions in vitiligo patients are the result of destruction and/or inactivation of the melanin-producing melanocytes. Keratinocytes still migrate to the surface of the epithelium, albeit without their cargo of pigment. This results in patches or macules on skin that look milky-white because they are devoid of pigment.[15, 16]

3. VITILIGO

Vitiligo is common acquired, non-contagious skin depigmentation that can appear anywhere on the body. Today vitiligo is not a rare disease. Its frequency continues increase in the world. Patients who suffer from face aesthetic discomfort that sounds psychologically on their socio-professional life. Females affected by vitiligo are more embarrassed and psychologically stressed than male patients. This situation has a severe impact on their life with impaired personal relationships and sexual activities and limitations in clothing choices. In Asia, particularly in India, vitiligo is considered a severe invalidating social stigma. In addition to this, vitiligo patient's skin becomes sensitive to the sun and is no longer a barrier to sunlight, which exposes the risk of melanoma. Vitiligo is therefore currently considered dermatology as a severe dermatitis.[17, 18]

Vitiligo the "Small blemish" was first noted in the Old Testament, Koran and Buddhist literature in approximately 1500 B.C. Despite a long history of this dermatosis, its exact etiology remains unknown. Celsus used the term vitiligo first time in his medical treatise, De Medicina.[19, 20] However, detailed clinical features of vitiligo were first described by both Brocq and Kaposi in early ninety.[21]

4. EPIDEMIOLOGY

More than 150 million people worldwide suffer from vitiligo. No country is immune, although each has different prevalence rates.[22] India shows the highest incidence in the world (up to 8.8%).[23] However, it is difficult to get a true picture of the prevalence of vitiligo. The largest epidemiological study of the prevalence of vitiligo is based on 47,033 inhabitants of the island of Bornholm in Denmark, showing an incidence of 0.38%.[24] The worldwide population of vitiligo prevalence is 0.1% to 2%. Though vitiligo can develop at any age but in 70% to 80% cases, it arises before the age of 30.[25]

5. CLASSIFICATION OF VITILIGO

Several classification systems have been proposed in literature. Most of them are based on the distribution or localization of the depigmented lesions. Because the etiology and pathogenesis of vitiligo are still unknown or uncertain, the question of whether vitiligo should be classified as a disease or a spectrum of disorders becomes central to its classification and management. According to Hercogová *et al*.,[26] vitiligo is classified as under: (Table 1.) When progression, prognosis, and treatment are considered, vitiligo can be classified into 2 major clinical types: segmental and nonsegmental. The first type matches totally or partially with acutaneous segment or (dermatomal distribution). It is characterized by white patches with rapid onset and involvement of the hair follicle pigmentary system. The course of segmental vitiligo can arrest and depigmented patches can persist unchanged throughout the life of the patient. This form is related probably to a dysfunction of the sympathetic nerves. The second type of disease seems to be more associated with systemic involvement. It includes all types of vitiligo except segmental vitiligo.[27, 28]

Table 1: Classification of Vitiligo.

NOMENCLATURE	SUBTYPE	CHARACTERSTICS
Localized	Focal	One or more macules in one area, but not clearly in a segmental distribution
	Unilateral/Segmental	Unisegmental- one or more macules distributed on one side of the body Bisegmental- Two segmental lesions distributed either unilaterally or bilaterally Plurisegmental- Multiple segmental lesions distributed either unilaterally or bilaterally
	Mucosal	Exclusive involvement of the oral or genital mucosae
Generalized	Vulgaris	Scattered patches that are widely distributed with a symmetrical pattern.
	Acrofacialis	Distal extremities and usually limited to face, head, hand and feet
	Mixed	Acrofacialis and Vulgaris
Universalis	-	Complete or nearly complete depigmentation (>80%)
Special forms	Trichromevitiligo	Skin appeared in three shades
	Quadrichrome	Four shades of pigment appeared viz white, pale brown, dark brown, and normal skin
	Inflammatory	Infected patches have inflamed red border

6. ETIOPATHOGENESIS

Numerous hypotheses have been recommended to give an explanation for the pathogenesis of vitiligo. None of these hypotheses can absolutely explain all the clinical and experimental observations made on this disorder. The most acceptable theories for the pathogenesis of vitiligo are.

6.1 Genetic hypothesis

Most of the human diseases are the outcome of an interaction between genetic variants and environmental factors and to establish the actual contribution of genetic factors is the first step of genetic studies that evaluate complex diseases.

Genetic epidemiological studies have demonstrated that vitiligo can be considered a complex genetic disease because: (i) the disease vary in symptom rigorousness and the age of onset, which hampers the definition of the appropriate phenotype and the selection of the most favourable study population; beginning of disease in the early age was associated with familial occurrence of generalized vitiligo.[29,30] Early onset vitiligo is also coupled with more severe disease; (ii) the etiological mechanisms of the disease can vary; vitiligo's etiopathogenesis has not yet been fully clarified, and several theories have been proposed; (iii) More oftenly, the complex genetic diseases are oligogenic or even polygenic and each gene takes part to a fraction of the overall relative risk.

Genetic factors are involved in the susceptibility of vitiligo as evident by familial studies, which revealed that vitiligo segregates with a complex standard of multifactorial and polygenic inheritance. Studies of Ando et al.,[31] concluded that there was a significant association between HLA-B46 and familial non segmental vitiligo in 131 Japanese patients, whereas HLA-A31 and CW4 were found in nonfamilial patients.

Currently, over 50 candidate genes were already investigated in association studies for susceptibility to vitiligo. But, some genes are only present a clear association with vitiligo. On one side, there are non-HLA genes, including DDR1, XBP1, NLRP1, PTPN22 and COMT; on the another side, there are HLA associated genes, including HLA-A2, HLA-DR4 and HLA-DR7 alleles.[32, 33]

In summary, genetic factors probably play a key role in the pathogenesis of vitiligo. The exact genetic defects remain to be identified.

6.2 Autoimmune Hypothesis

Autoimmune hypothesis is one of the most important and popular. This hypothesis suggests that destruction of melanocytes is the outcome of abnormal immune system. Large amount of considerable data involve immune mechanisms in the pathogenesis of vitiligo and signify that vitiligo may share common linkages with other autoimmune diseases including Addison's disease, thyroid disorders, juvenile diabetes mellitus etc.[29, 34]

Vitiligo is escorted by abnormal cellular and humoral immunity. Serum circulating autoantibodies mostly of the IgG class in an elevated level have been noticed in 5-10% of vitiligo patients. Though, the function of antimelanocyte antibodies in pathogenesis of vitiligo remain uncertain and it has has been recommended that their presence may be secondary to melanocyte and keratinocyte damages.[35, 36]

A mild mononuclear cell infilterate can be observed in the margins of lesional and normal pigmented skin of patients with active vitiligo or inflammatory vitiligo.

Immuno histochemical studies revealed that it is T cells that are abundant in these infiltrates; T cells may thus play a significant role in the destruction of melanocytes. Recently, an *in vitro* study indicated that cytotoxic T lymphocytes infiltrated in common vitiligo perilesional area wiped out neighbouring melanocytes.[37, 38]

Diversified abnormalities in peripheral blood mononuclear cells have also been elucidated. Levels of CD 4+, CD8+, and natural killer cells have been reported to be normal, increased or decreased. These parameters are influenced by various factors and they are not standardized in any of the studies conducted.[39]

6.3 Neural Hypothesis

Lerner[40] was suggested neural hypothesis for the first time. It was reported that there are certain neurochemical mediators secreted from nerve endings are cytotoxic to pigment cells. This theory is supported by the following clinical observations.

1. The existence of the localized vitiligo that seems to be limited to one segment of the body. This 'segmental' vitiligo is approximately non dermatomal but normally affects portions of multiple dermatomes. It is also proposed that segmental vitiligo does not act in response to classical vitiligo therapies, such as PUVA, but to agents that modulate neural function.
2. Vitiligo onset is reported during a period of emotional stress. However the mechanism by which stress results into depigmentation is not yet clear.
3. It is also assumed that the patients with neurological disorders come out with vitiligo, in a child with viral encephalitis, in multiple sclerosis and in a patient with peripheral nerve injury.[41]

6.4 Auto cytotoxic Hypothesis

According to this theory the precursors formed during melanogenesis are toxic to melanocytes. Melanocytes are having an intracellular protective meachanism in order to eliminate toxic melanin precursors (e.g. dopa, dopachrome and 5, 6-dihydroxyindole) and free radicals. In case of vitiligo, there may be some interference in this mechanism, as a consequence free radicals and indoles are accumulated which destruct melanocytes.[42]

6.5 Growth factor defect Hypothesis

In 1987, Puri *et al*., hypothesized that the defective growth of melanocytes began from non lesional and peri lesional skin. More interestingly some investigators found that he defects were partially corrected by in vitro supplementation of fetal lung fibroblast derived growth factors. Their finding reveals that growth defects play a crucial role in vitiligo pathogenesis. However, further studies are required to assess the use of growth factors, as a part of repigmentation therapy in vitiligo.[43]

6.6 Adhesion Defect Theory

Gautier et al., in 2003[44] postulated that non segmental vitiligo might be caused by a chronic detachment of melanocytes stimulated by trauma, chiefly by a mechanical rubbing of healthy skin. This concept is called as "melanocytorrhagy theory". Additionally, Gauthier et al.[45] proposed that an autoimmune activation could be stimulated by memory T cells or dendritic cells detecting auto-antigens during melanocytorrhagy through the epidermis basal layer.[45]

6.7 Convergence Theory

It has been assumed that a combined theory rather than a separate theory is more suitable to predict the etiology of vitiligo. Furthermore, the studies that the patient's exhibit a variety of clinical forms and various histories of onset of disease makes us to believe that the aetiology of vitiligo may differ among individual patients. This theory reveals that genetic factors, stress, accumulation of toxic compounds, autoimmunity, mutation, infection, varied cellular environment, impaired melanocyte accumulation and distribution can all contribute to the phenomenon of vitiligo.[46]

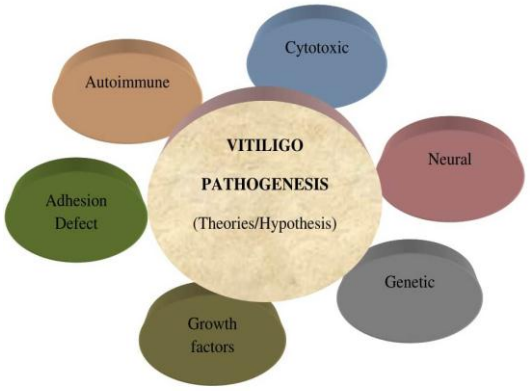

Figure 1: Theories of vitiligo pathogenesis.

7. TREATMENT FOR VITILIGO

Vitiligo is a chronic condition that lasts for a lifetime. The disadvantages of Vitiligo are, on one hand, the unsightly contrast between affected skin and normally pigmented skin and on the other hand the photosensitivity of the untreated depigmented skin which can result in burns and skin cancer. The ideal treatment should stop the spread of the disease and cause an aesthetically acceptable repigmentation.

7.1 NON SURGICAL TREATMENT

A variety of nonsurgical treatment regimens are currently employed in vitiligo. All nonsurgical treatments have been used to repigment or depigment the skin; however, many of them require a prolonged treatment course and may yield minimal results as well as carry unwanted side effects. Widely used nonsurgical treatment modalities are demonstrated here under.

7.1.1 Topical Therapy

7.1.1.1 Topical corticosteroids

Topical steroids (TCs) are still the basis of treatment for vitiligo. Though they possess numerous side effects, such as atrophy or telangiectasia, TCs are considered as first

line therapy for localized forms of vitiligo because of their wide availability, low cost and efficacy.[47] These rarely achieve more than 50–75% repigmentation and are cumbersome, requiring multiple daily applications. They may require a year or more to note significant improvement.[48] Left-right study found that combined therapy with tretinoin plus topical corticosteroids is safe and effective for treatment of patients with vitiligo.[49]

7.1.1.2 Topical Immunomodulators

Topical Immunomodulators are novel therapeutic agents that act via immunologic pathways either to suppress or to enhance immune and inflammatory reaction in the skin. The inhibitory topical immunomodulators, tacrolimus and pimecrolimus, are used for treatment of vitiligo. The primary mechanism of action in these drugs for the treatment of vitiligo involves calcineurin inhibition which leads to down regulation of antigen-specific T-cell reactivity and interruption of the transcription of genes for a range of proinflammatory cytokines important in the pathophysiology of the early immune response.[50] Compared to TCs, topical calcineurin inhibitors (TCIs) do not provoke skin atrophy.[51] Topical tacrolimus 0.03% or 0.1% is not associated with the adverse events that have been observed with the oral administration of the drug.[52] Recently, a study found that tacrolimus has better clinical efficacy during the active stages of vitiligo[53] Tacrolimus 0.1% ointment and pimecrolimus 1% cream have defined roles in the treatment of vitiligo.[54]

7.1.1.3 Topical vitamin D3 analogues

Calcipotriol have been used as monotherapy or in combination with phototherapyfor the treatment of vitiligo. This possible mechanism prevents skin T cell infiltration, which is involved in the pathogenesis of vitiligo.[55] It is also effective when used in combination with TCs, especially in difficult-to-treat areas such as the eyelids. However, the true effects of vitamin D analogues on vitiligo remain controversial.[56]

7.1.2 Phototherapy and Photochemotherapy

Patients having extensive depigmentation are recommended treatment with light therapy because of the large surface area affected. Light therapies include.

1. Oral or topical psoralns plus ultraviolet A radiation (PUVA),
2. Narrow band ultraviolet B radiation (NB-UVB)
3. Broadband ultraviolet A (BB-UVA)
4. Monochromatic excimer light (MEL)

Ultraviolet (UV) radiation is considered the first line of therapy for vitiligo that achieves partial repigmentation in 50–80% of patients.[51, 57]

7.1.2.1 PUVA

Photochemotherapy is a therapeutic method that consists of the use of a drug that enhances the effects of light. In PUVA therapy there is a need of UVA (320-400 nm) and a photosensitizing drug such as8 methoxypsoralen. Although it is effective for the treatment of vitiligo but it is found associated with some adverse effects like risk of squamous cell carcinoma of the skin, cutaneous phototoxicities and nausea. Hence, NB-UVB is more preferable than PUVA therapy.[58, 59]

7.1.2.2 Broadband ultraviolet A (BB-UVA)

A randomized controlled trial done by El Mofty *et al*.,[60] found that BB-UV at a dose of 15 J/cm^2 per session confers result for vitiligo that are comparable with PUVA, but still requires further studies. El-Mofty *et al*.,[61] also estimated that BB-UVA is more efficacious than NB-UVB for the treatment of vitiligo. So, BB-UVA may be considered as an alternative strategy for vitiligo treatment.

7.1.2.3 NB-UVB

Monotherapy with NB-UVB (311–312 nm) was introduced in 1997 and now considered as effective and safest type of therapy forgeneralized vitiligo, with better repigmentationand fewer adverse effects than PUVA.NB-UVB alone reaches repigmentation rates between 41.6% and 100%[49] Recently, a study found that NB-UVB phototherapy may be efficient treatment option for vitiligo patients at an early onset of disease. Psoralen-NB-UVB is more effective than NB-UVB phototherapy because it requires less cumulative dose, producing a greater percentage reduction in vitiligo area severity index scores and the response start earlier.[62]

7.1.2.4 Monochromatic excimer light (MEL)

The MEL has proved to be a useful tool in the treatment of vitiligo. Patients treated with excimer laser are achieving excellent results in a matter of a few months rather than many months to years. The combination of monochromatic excimer light with xenon chloride gas emits light with a wavelength of 308nm.[63] Several papers reported high success rates of successful results when it is used alone. Indeed, response rates as high as could 95% were achieved.[57] It was also highlighted that MEL produced better outcomes than NBUVB.[64]

7.1.3 Depigmentation Therapy

Depigmentation therapy involves the removal of pigmented skin in a case of universal, extensive vitiligo. Q-switched laser therapy is more effective in patients with active vitiligo than patients with stable vitiligo and with no long-term side effects. Topical application of 20% monobenzyl ether of hydroquinone (MBEH) was also effective.[65, 66]

7.1.4 Direct electrical current therapy

Direct electrical current delivered by Baghdadin device. Direct electrical current is an effective method to induce melanogenesis in patients with vitiligo. The mode of action of direct current is not well understood but it might be related to its immunomodulatory effect, its effects on the inflammatory cells movement and on the expression of cellular receptors.[67]

7.2 SURGICAL THERAPY

Surgical melanocyte transplantation is an important therapeutic option available for patients with stable disease who have failed medical treatments. They are typically used for difficult-to-treat areas like hands, feet, lips and nipples.[68] Tissue grafting and cellular suspensions are the two main melanocyte transplantation techniques currently offered for stable vitiligo. Tissue-grafting techniques include full thickness punch grafts, blister grafts and split-thickness skin grafts. Cellular grafting consists of cultured or non-cultured epidermal suspensions.

7.2.1 Punch grafting

Punch grafting is performed by transplanting 1–2 mm full thickness punch biopsies of normally pigmented skin into areas affected with vitiligo. Malakar *et al*.,[69] reported 90% to 100% repigmentation rates in 74.5% of the patients treated. In addition, NB-UVB could be combined with punch grafting toobtain even better results.[70] It is time consuming and has potential adverse effects, including cobble-stoning and scarring, especially at the donor site.[71]

7.2.2 Blister graft technique

Epidermal blister or blister graft technique involves the creation of a sub epidermal bulla from the donor site performed with either liquid nitrogen or topical PUVA. The roof of the bulla is then collocated into the recipient area, prepared to allow the uptake of the graft using different techniques to obtain an abraded surface. Several procedures to obtain the bulla have been reported in the literature.[72]

7.2.3 Split thickness grafting

Split thickness grafts involve mechanical or chemical dermabrasion of the depigmented recipient skin to remove the superficial epithelium followed by a split-thickness biopsy of normally pigmented donor skin. A dermatone is required to acquire a uniform skin graft. Agarwal *et al*.,[73] said that it is now possible to attain repigmentation rates up to 100%. As dermatone is not easy to use, an expert surgeon is needed to handle it.

7.2.4 Cultured melanocyte grafting

In the era of cell based therapies, the strategies may involve culturing melanocytes to treat a variety of pigment disorders, such as albinism and vitiligo. Cultivation of melanocytes *in vitro* can increase the cell number dramatically and cells from a small piece of normal skin can be used to treat large depigmented areas.[74] This technique is definitely beneficial to the patient but having certain limitations such as time consuming, expensive and also has risk of transmission of viral infections and the development of malignancy. Non culture grafting on the other hand can be performed faster with equivalent or better results.[75]

7.3 Stem cells in treatment of vitiligo

Skin is an easily accessible source of various sub population of stem cells including epidermal stem cells, hair follicle stem cells (HFSCs) and dermal mesenchymal stem cells (DMSCs). The outer root sheath (ORS) of the hair follicle is a rich source of a type of HFSCs called the melanocytes stem cells (MelSCs). These HFSCs have a vast, unexplored potential in the treatment of vitiligo as initial re-pigmentation often occurs around the hair follicles. Common therapeutic modalities such as tacrolimus, phototherapy and dermabrasion acts through MelSCs. DMSCs inhibit T-cell proliferation and induce T-cell apoptosis. Studies have shown that DMSCs modulate the infiltration of peri-lesional CD8+ T-cells. They inhibit CD8+ T-cell proliferation, induce their apoptosis and regulate their cytokines/chemokines production. Thus DMSCs might be used as auxiliary agent to improve transplantation efficacy in patients undergoing noncultured/cultured autologous melanocyte transplantation.[76, 77]

Newer cellular techniques have explored the use of ORS hair follicle suspension in surgical treatment of vitiligo. Advancement in melanocyte and stem cell research has identified various cytokines, growth factors and regulators involved in proliferation and differentiation of melanoblasts, which can be used for autologous *in situ* melanocyte regeneration.[78]

7.4 Future therapies

In future, gene therapy will be a possible treatment, with research into the pathophysiology of vitiligo.[62] Various studies are assessing the evidence and safety of combining phototherapy with different antioxidants like capsaicin, piperidine, L-carnosine and curcumin. Several other potential agents currently under investigation include statins, basic fibroblast growth factors, prostaglandin E2 analogues and COX-2 inhibitors.[79, 80] CO2 laser, micrografting, microphototherapy, the utilisation of melanocytes from the outer root sheath of hair follicles and dressings post-vitiligo surgery are also being investigated.[81]

In the future, treatment with low-dose cytokines-based therapy represents an opportunity for the dermatologists to overcome some specific pitfalls of currently available therapeutic protocols. The association between LDM and classic topical treatments within an overlapping strategy paves the way to a more effective therapeutic approach to vitiligo.[74, 81]

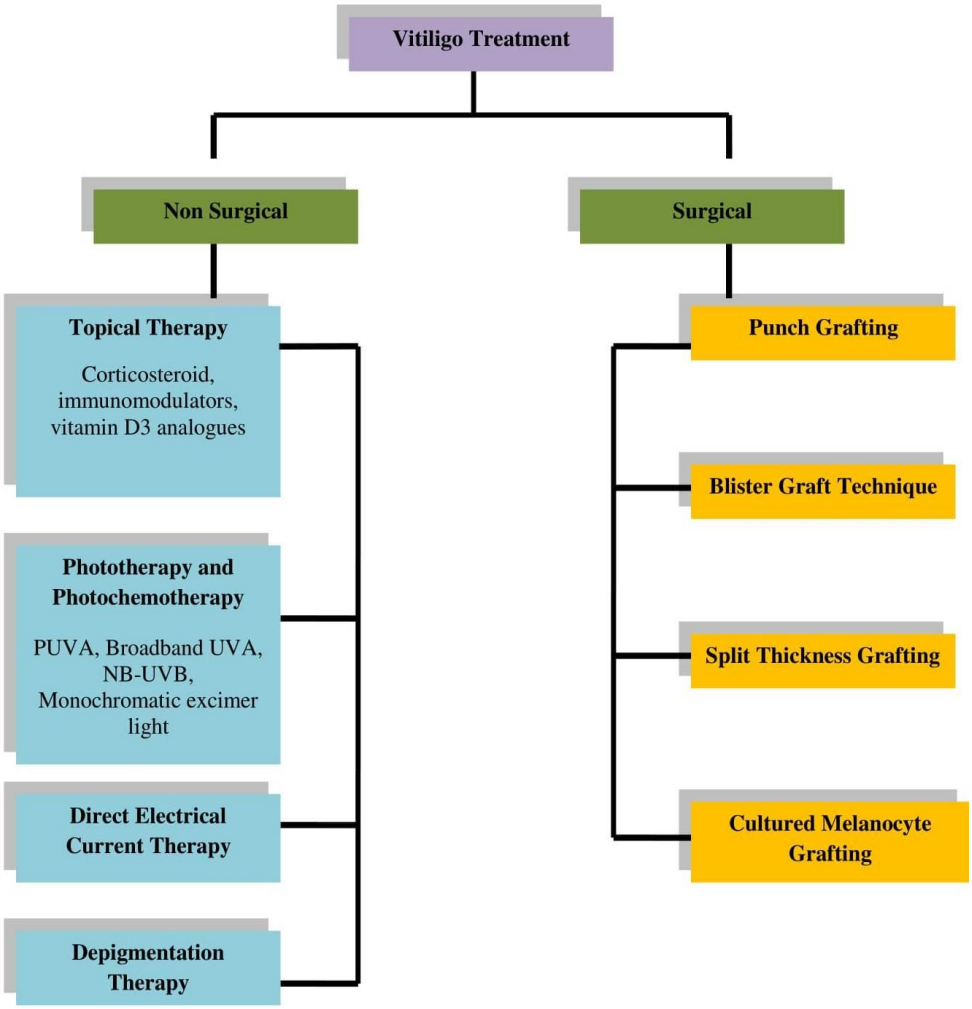

Fig. 2: Different treatment strategies for vitiligo.

8. CONCLUSION

Vitiligo is a common systemic disorder resulting from the loss of melanocytes in the skin and leads to psychological and social embarrassment in dark skin people. In conclusion vitiligo is considered to represent a complex reaction pattern or a disorder, involving multiple etiological factors. Because of its complexity, nowadays many therapies are available for obtaining a repigmentation. Since there is no consensus on the pathogenesis of vitiligo, a treatment to completely cure vitiligo does not exist. Problem with treatment is associated with slow effects and longer duration, also due to some side effects patients get frustrated and discontinue the treatment. However, there is still a need of an innovative and effective therapeutic approach for vitiligo treatment.

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