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Vitiligo: A persistent enigma

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1. Introduction

Vitiligo is a depigmentation disorder characterized by amelanotic skin patches, which may change shape and size with time, at times, leading to complete depigmentation of skin [1]. Hypopigmentation of the skin is attributed to the loss of epidermal melanocytes [2]. The disorder is associated with other co-morbidities like audiologic abnormalities [3] and lipid profile abnormalities [4]. There is a strong co-relation with autoimmune co-morbidities like psoriasis, thyroid disorders, rheumatoid arthritis, type I diabetes mellitus, alopecia areata, inflammatory bowel disease and systemic lupus [5]. The disease has socioeconomic implications and due to its cosmetic manifestations, bears adverse psychological impact on the patient [2]. Worldwide incidence of the disease is predicted to be 0.5 to 2% [6].

The disease has a number of overlapping aetiologies ranging from epidermal to subcellular and systemic levels, hence multiple theories have been put forth to explain etio-pathogenesis of vitiligo. Autoimmunity, oxidative stress, genetic predisposition, stressful conditions, morphological and functional changes in keratinocytes, damage to melanocytes, reduced melanocyte proliferation and migration and alterations in extracellular matrix leading to loss of melanocytes are multiple etio-pathological factors leading to the development and progress of vitiligo [1]. Multiple treatment options are available, including oral and topical corticosteroids, calcineurin inhibitors, psoralens + UVA (PUVA), narrow band UVB, vitamin D analogues, L-phenylalanine, pseudocatalse. Surgical interventions are an option, when vitiligo is resistant to oral and topical conventional therapies. None of the approaches have been able to achieve the goal of complete and stable re-pigmentation. Effectiveness of various treatment modalities is less than desirable and their long-term use results in multitude of adverse effects. The problem is further aggravated by the chronic nature of the disease. Requirement of long-term treatment coupled with the repeated failure of treatment regimens affects patient compliance [7]. Thus, better treatment options are constantly being explored by the researchers.

ISSN:0971-1260
Vol-22-Issue-37-December -2019

One of the reasons behind the limited success of treatment regimens might be the fact that all the modalities are mutually exclusive. For a disease with multiple and overlapping etiopathologies, a multipronged approach is expected to yield better results. Present article provides a brief account of the various etio-patho-mechanisms contributing to the development and progression of vitiligo, available treatment modalities and their limitations. Advantage of using vesicular delivery systems in vitiligo therapeutics and use of a combination of drugs to target the disease with multiple etio-patho-mechanisms is also discussed.

1. Etiopathogenesis

A number of theories have been proposed to explain the etiopathogenesis of vitiligo. Autoimmunity plays a significant role in the development and progression of the disease. Autoantibodies to melanocytes are reported in the serum of vitiligo patients and animal models of vitiligo [8, 9]. Multiple proteins specific to melanocytes and melanosomes act as autoantigens resulting in the activation of immune system and generation of autoantibodies and thus play crucial role in the development of autoimmunity observed in vitiligo patients [10]. Cytotoxic T cells present in the perilesional area cause the destruction of melanocytes in vitiligo leading to hypo-pigmentation [11]. Cutaneous Leukocyte Antigen positive (CLA+) T cells also play dominant role in the destruction of melanocytes as CLA+ T cells have been reported to be co-localized with disappearing melanocytes in the perilesional skin of the vitiligo patients [12].

Strong evidence in the literature points towards increase in oxidative stress in the skin of vitiligo patients. Reduced levels of catalase (CAT) have been reported in the lesional and non-lesional skin of vitiligo patients [13], which probably contributes towards increased epidermal levels of H_2O_2. Dysregulation of biopterin pathway further causes melanocyte toxicity. Vitiligo patients are reported to have increased activity of the enzyme GTP-cyclohydrolase I leading to over synthesis of (6R)-L-erythro 5,6,7,8 tetrahydrobiopterin (6-BH4). Increased 6-BH4 levels result in the accumulation of its non-enzymatic by-product (7R)-L-erythro 5,6,7,8 tetrahydrobiopterin (7-BH4) in the epidermis of the patients as well as increased synthesis of catecholamines in the keratinocyte, which reflects in the increased levels of norepinephrine (NE) in plasma and urine of vitiligo patients. Melanins are biosynthesized by melanocytes from the precursor amino acid L-Phenylalanine, which is converted to L-Tyrosine by the action of enzyme phenylalanine hydroxylase. 7-BH4 acts as a competitor inhibitor of phenylalanine hydroxylase resulting in the reduced production of L-

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Tyrosine. In addition, inhibition of this crucial enzyme also leads to the production of H_2O_2. Reports indicate that H_2O_2 can destabilize tetrahydropyrrole ring of catalase in the presence of UV light. Thus, increased production of H_2O_2 could have correlation with reduced catalase activity in vitiligo patients [14]. Increased NE levels in vitiligo skin have also been predicted to contribute towards pathogenesis of the disorder. NE metabolism by Monoamine oxidase is associated with increased H_2O_2 generation and hence increased oxidative stress leading to melanocyte damage [15]. Incidence of disease has strong co-relation with the genetic make-up of the patient. Approximately 36 vitiligo susceptibility loci have been identified till date, of which about 90% of genes encode immunoregulatory proteins and approximately 10% encode melanocytic proteins [16]. Changes have also been observed at cellular level in vitiligo skin. Adverse morphological changes have been reported in keratinocytes [17]. Reduced levels of basic fibroblast growth factor (bFGF) have been reported in this depigmentation disorder. bFGF is the natural growth factor for melanocytes and its reduction has been proposed to be the cause of depigmentation in vitiligo [18].

3. Available treatment options

Multiple approaches have been tried to treat vitiligo. Lesions on face and neck are more amenable to medical treatment as compared to those on extremities and trunk, whereas the lesions on acral parts of extremities, wrist, feet, male genitals etc. are most difficult to treat [19]. Various treatments options available are:

3.1 Corticosteroids

Topical corticosteroids are used as first line treatment for vitiligo as they are easy to use and are inexpensive relative to other treatment modalities [20, 21]. Generally moderately potent to highly potent topical corticosteroids are employed, which have been found to be effective in adult vitiligo patients. In a study conducted in children, re-pigmentation could be achieved in 64% of patients, but systemic absorption of the steroids could not be ruled out [22]. The local side-effects associated with their use include skin atrophy, acneiform eruptions, striae, telangiectasia, hypertrichosis etc. while their systemic absorption may cause adrenal suppression, hyperglycemia and rarely posterior sub-capsular cataracts [23].

Oral minipulse therapy (OMP) has been tried with betamethasone and dexamethasone [24]. Although it stops further progress of the disease, it does not cause re-pigmentation. Long term use of systemic corticosteroids is associated with a number of adverse effects [13]. In addition, relapse with OMP is quite common especially in younger population [21].

ISSN:0971-1260
Vol-22-Issue-37-December -2019

3.2 Immunomodulators

Topical calcineurin inhibitors like tacrolimus have been found to be beneficial in vitiligo. Tacrolimus inhibits the activation of T cells and thus affects subsequent production of cytokines [25]. Studies have shown tacrolimus and pimecrolimus to possess comparable efficacies to topical corticosteroids in the therapy of vitiligo [26]. There were no significant differences found in the efficacy of topical tacrolimus and pimecrolimus. Both topical calcineurin inhibitors were found to be especially beneficial for the lesions on face. Side-effects include burning sensation, pruritis, erythema and higher infection rate e.g. herpes simplex and eczema herpeticum.

Oral immunosuppressants have not been found to be of value in the therapy of vitiligo. Systemic cyclosporin did not produce re-pigmentation in majority of the patients even after several months of treatment, but induced adverse effects like renal dysfunction and hypertension [27]. Anti-tumour necrosis factor- α (TNF-α) etanercept was tried in four vitiligo patients at the dose of 50 mg/Kg s.c. for 12 weeks followed by additional four-week therapy at the dose of 25 mg/Kg s.c., none of the patients showed re-pigmentation [28].

3.3 Photochemotherapy

Psoralen combined with Ultraviolet-A (PUVA) has been used for the treatment of vitiligo, where psoralen is used along with long wave UVA radiation (320-340 nm). Psoralen is given either orally or topically in the form of cream, solution or in bath followed by exposure to UVA (320-340 nm) [13]. 5-Methoxypsoralen and 8-Methoxypsoralen have been tried with UVA therapy. Both are equally effective, but total UV exposure required with 5-Methoxypsoralen is more as compared to 8-Methoxypsoralen. Oral administration is generally done 1-3 hours and topical application is done 30 minutes prior to UVA exposure. Adverse effects after oral administration are nausea, vomiting and retinal toxicity in children below 10 to 12 years of age. Cutaneous reactions include pruritis, erythema, xerosis, burning with blistering [13]. Rarely PUVA therapy has also resulted in PUVA burns leading to prurigo nodularis [29]. Psoralens are basically furocoumarins. After photoactivation, they react with pyrimidines of DNA resulting in dimer formation. This results in the proliferation of melanocytes, increased tyrosinase synthesis, increased melanin synthesis in melanosomes and subsequently increased transfer of melanosomes to keratinocytes. Limited success is reported with PUVA therapy. Complete repigmentation is observed in only 20% of the treated patients and relapse rate is high with approx. 75% of patients relapsing after 1 or 2 years of treatment [13].

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Use of Khellin with UVA (KUVA) has also been tried [30]. Long term KUVA treatment induces re-pigmentation comparable to PUVA therapy. Khellin can be administered two hours prior to UVA exposure orally and topical application in the form of cream or gel can also be done. Main toxicity of KUVA is liver toxicity, which is observed in approximately 30% of the treated patients [13].

3.4 Narrowband Ultraviolet B (UVB)

Narrowband UVB therapy is considered to be safe and can be used even in children. Light at wavelength 311 nm is considered narrowband UVB and vitiligo responds best at this wavelength [31]. Narrowband UVB has been found to be more effective than topical PUVA. The combination of narrow band UVB with other treatment modalities has been tried. The results are conflicting, where one study showed that pseudocatalase cream along with UVB did not confer advantage in terms of increased efficacy when compared to UVB alone [32], other study reported narrowband UVB activated pseudocatalase to be better treatment option as compared to UVB alone. The combination of UVB and calcineurin inhibitors has been reported to be promising for inducing re-pigmentation in vitiligo patients [33].

3.5 Excimer

Excimer laser of 308 nm is more effective in the treatment of localized vitiligo as compared to normal phototherapy, although it cannot be used in case of widespread lesions. Its efficacy can be enhanced by co-application of corticosteroids or calcineurin inhibitors [34]. Studies have shown that 308 nm excimer laser along with 1% pimercrolimus cream is more effective as compared to excimer therapy alone [35]. Disadvantages with excimer therapy are that it may cause blisters, erythema and hyperpigmentation. Long term exposure to UV radiations may result in ageing and cancers.

3.6 Helium-neon laser

Treatment with helium-neon laser resulted in re-pigmentation in 60% of patients, but complete re-pigmentation was observed in only 7.5% of patients. It has been postulated to improve cutaneous microcirculation [36]. Enhanced melanocyte proliferation due to helium-neon laser exposure is because of increased expression of $\alpha 2\beta 1$ integrin. This results in upregulation of phosphorylated cyclic-AMP response element binding protein.

3.7 Pseudocatalase

Vitiligo patients exhibit reduced catalase activity in their epidermis [37], resulting in higher H_2O_2 stress. Promoter variant in catalase gene was found to make the individuals genetically more pre-disposed to vitiligo in a Chinese population [38]. Increased oxidative stress might

ISSN:0971-1260
Vol-22-Issue-37-December -2019

be due to the imbalance between the generation of hydrogen peroxide and levels of catalase enzyme [39]. These observations support the use of pseudocatalase as a therapeutic intervention for vitiligo. However, there are conflicting reports regarding the efficacy of pseudocatalase in vitiligo. Few of the studies reported no significant benefit with the use of pseudocatalase, whereas some reports indicate the beneficial effects of pseudocatalase.

3.8 Vitamin D analogues

Vitamin D is a hormone synthesized in the skin and plays an important role in melanogenesis. 1 alpha, 25-dihydroxyvitamin D3 stimulated melanin synthesis in B16 mouse melanoma cells [40]. Vitamin D3 has been found to increase the tyrosinase levels in cultured human melanocytes. Topical Vitamin D gives better results when used with phototherapy. It also decreases the expression of cytokines that play role in the pathogenesis of vitiligo, thus might prevent the destruction of melanocytes [41]. In one of the studies, the efficacy of topical calcipotriol and narrowband UVB was found comparable to the combination of topical calcipotriol, narrowband UVB and betamethasone [42]. The combination of calcipotriene and betamethasone dipropionate in the form of ointment was found to give promising results [43]. High dose of oral Vitamin D3 (35000IU, once daily for six months) was tried in 16 vitiligo patients, of which 14 showed 25-75% re-pigmentation.

3.9 L-Phenylalanine

The conversion of L-Phenylalanine to L-tyrosine in melanocytes by phenylalanine hydroxylase is an important step in the initiation of melanogenesis. This reaction provides the majority of tyrosine for melanin synthesis [44]. *In vitro* studies involving primary epidermal melanocytes from vitiligo patients provided evidence for reduced L-phenylalanine uptake and turnover in these cells [45]. L-phenylalanine resulted in improvement of vitiligo lesions when used in combination with clobetasol propionate and UVA. In another study, a topical gel containing phenylalanine, *cucumis melo* extract and acetyl cysteine was found to be beneficial [46].

3.10 Surgical Interventions

Surgical treatment can be tried when vitiligo is resistant to the traditional therapies. Primary requirement for surgical interventions is stability of vitiligo lesions i.e. absence of new lesions for at least past two years and absence of Koebner phenomenon [19]. Epidermal transplants and transplants of cultured melanocytes can be done.

Epidermal blister graft or suction blister graft involves creation of blisters by generating negative pressure in area with normal pigmentation [47]. After separation of epidermis from

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Vol-22-Issue-37-December -2019

dermis, the pigmented epidermis is harvested and transplanted to previously denuded achromic are.

Autologous split-thickness punch graft includes transplanting small thin explants from pigmented areas to achromic areas [48]. Circular epidermal fragments of 1-1.2 mm diameter are removed from the recipient area with a punch biopsy device under the influence of local anaesthetic. Explants of same dimensions are removed from normal pigmented area, transferred to recipient area and fixed with sterile surgical adhesive and bandaged. Larger epidermal strips can be transplanted, but this can result in graft retraction [49]. The recipient area can also be prepared using pulsed erbium: YAG laser. This technique has the highest success rate in terms of re-pigmentation, but is associated with side-effects like milia, scarring and hyperpigmentation [50].

Full thickness punch graft technique involves grafting of full thickness explants. Under the influence of local anaesthetic, recipient bed is prepared employing a biopsy punch, explants are taken from the normochromic area. Grafted tissue is fixed with the help of sterile adhesive, covered with a paraffinized gauge and a suitable bandage. Exposure to UV-A radiations or sunlight stimulates the migration of melanocytes from the grafted tissue, ultimately leading to complete re-pigmentation in the majority of cases [51].

Cellular grafts are composed of autologous suspension of dissociated keratinocytes and melanocytes. A thin lamina of skin is incubated with trypsin solution and the resulting dissociated epidermal cell suspension is injected in the liquid of suction bubbles in depigmented areas. Transplantation of keratinocytes along with melanocytes ensures better establishment of melanocytes [52]. Melanocyte enriched epidermal cell suspension can also be applied to dermobraded depigmented area and covered with thin collagen film. This method is useful in the treatment of several small depigmented areas.

The transplants of cultured melanocytes have also been employed for treating vitiligo [53]. A small thin skin lamina is dissociated enzymatically and the cells are incubated in a medium that is selective for melanocyte proliferation. The cultured melanocytes are then applied to dermobraded achromic area and are fixed with collagen film.

3.11 Depigmentation

In patients with extensive and refractory vitiligo, depigmentation can be employed. One of the common depigmenting agents is monobenzylether of hydroquinone (MBEH), which causes irreversible depigmentation [54]. But MBEH takes months to depigment the skin. Other agents that are used are 4-methoxy phenol and 88% phenol. Some physical therapies

ISSN:0971-1260
Vol-22-Issue-37-December -2019

for depigmentation are also available like Q-switched ruby, alexandrite lasers and cryotherapy. Q-switched 755 nm ruby laser can be used alone or in combination with methoxyphenol. It adversely affects melanin and melanocytes.

4. Limitations of current therapy

Main problems with various available therapies are:

1. Steroids: Topical steroids can cause atrophy, acneiform eruptions, striae, telangiectasia, hypertrichosis etc. and systemic absorption of steroids may cause adrenal suppression, hyperglycemia and rarely posterior sub-capsular cataracts.
2. Calcineurin inhibitors: burning sensation, pruritis, erythema and higher infection rate e.g. herpes simplex and eczema herpeticum.
3. PUVA: Oral administration may cause nausea, vomiting and retinal toxicity in children below 10 to 12 years of age. Cutaneous reactions include pruritis, erythema, xerosis, burning with blistering and PUVA burns leading to prurigo nodularis. Only 20% of the treated patients show complete re-pigmentation, relapse rate high. long term exposure may lead to ageing and cancers.
4. KUVA: liver toxicity, long term exposure may result in ageing and cancers.
5. Narrowband UVB: less effective when used alone.
6. Excimer: Not useful for widespread lesions, may cause blisters, erythema and hyperpigmentation. Long term exposure can cause ageing and cancers.
7. Helium-neon laser: Complete re-pigmentation in only 7.5% of treated patients.
8. L-Phenylalanine, pseudocatalase, vitamin D analogues: Less and variable efficacy.
9. Surgical treatments: Require skillful personnel to do the surgeries. Side effects include milia, scarring, hyperpigmentation, cobblestone appearance, invasive nature of treatment methodology, transplants of autologous cultured melanocytes may cause carcinogenicity.
10. Depigmentation: Skin sensitization, eczema, burning sensation, dermatitis.

Conclusion

Although multiple treatment modalities are available for treating vitiligo patients, none of them has been able to achieve the goal of complete re- pigmentation in patients. The overall success rate has been low and variable. Stability of re-pigmentation is another issue; reversibility of re-pigmentation also has been a cause of concern [3]. The disease, so far, has

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Vol-22-Issue-37-December -2019

been found to be refractory to all existing treatment modalities. Due to the nature of the disease, long term therapy is advocated in most of the cases. Thus, side-effects of the drugs become another limiting factor.

Patient compliance to available therapies is limited by side effects, long term duration of treatment and cost factor; thus, further reducing the efficacy of treatment. Hydration of stratum corneum is reported to be significantly low in vitiligo. Moreover, for a disease with multiple etiopathogenesis, if the treatment plan is multi-pronged, the therapy can prove to be more effective.

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