Faridpur Med. Coll. J. 2017;12(1):34-39

Review Article

Vitiligo Management- An Update

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Abstract:

Vitiligo is an acquired, often progressive disorder of hypopigmentation. A lot of research has been conducted during the years yet its exact etiology still remains elusive. As a result even after so many years, there is no ideal treatment for vitiligo. Treatment options such as Narrowband Ultraviolet B (NB-UVB), Targeted Phototherapy, and Excimer laser on the medical front, in addition to epidermal cell transplantation and melanocyte culture transplants on the surgical front, have all revolutionized the management of this psychologically devastating disease.

Key words: Vitiligo.

Introduction:

Vitiligo is one of the oldest and commonest skin disorders affecting approximately 1-2% of the human population[1]. The disease shows no regard to the ethnic, racial or socioeconomic background of the affected sufferers. It is clinically manifested by circumscribed achromic macules often associated with leukotrichia (white hairs). So the cosmetic impact of this disease is tremendous and its psychological impact is devastating particularly in coloured races[2-4]. The aetiopathogenesis of this disease is now much better understood and a lot of new advances have been made on the therapeutic front as well. With these new therapeutic options, we are currently in a much better position to treat this disease than we were a decade or two earlier.

Classification of vitiligo:

There are no universally accepted classifications available for vitiligo. Classification suggested by Hercogova et al.[5] seems helpful.

(a) Localized- focal, unilateral/segmental, mucosal
(b) Generalized- vulgaris, acrofacialis, mixed
(c) Universalis and
(d) Special forms- trichrome, quadrichrome and inlfammatory.

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Aetiopathogenesis:

Both the genetic and epigenetic factors seem to play a role in the aetiopathogenesis of vitiligo. Recent studies have suggested that genetic factors play a major role. An alteration in the micro-environment of epidermal-melanin units, related possibly to immunological and neurochemical factors has also been presumed[6].

Various hypotheses proposed in the pathogenesis of vitiligo are -

1. Immune response hypothesis
2. Neural hypothesis
3. Autotoxic self-destructive or free radical hypothesis
4. Composite hypothesis
5. Melanocyte growth factor reduction hypothesis
6. Antioxidant deficiency theory
7. Melanocytorrhagy
8. Apoptosis of vitiligo melanocytes.

New advances in management:

Medical therapies

The most recent advances on the medical front have been Narrowband Ultraviolet B (NB-UVB) therapy, Targeted Ultraviolet B (UVB), Excimer laser therapies, topical immunomodulator treatment in the form of topical calcineurin inhibitors, topical pseudocatalase, and topical Vitamin D analogues in combination with Ultraviolet (UV) light.

NB-UVB

NB-UVB, using UV-lamps with a peak emission of around 311nm has now emerged as the treatment of first choice in generalized vitiligo as well as vitiligo vulgaris (patchy vitiligo)[7,8]. The efficacy of NB-UVB in vitiligo was first demonstrated by Westerhof and Nieuwboer-Krobotova in 1997[9]. Since then there have been a large number of clinical studies that have demonstrated the therapeutic benefit of NB-UVB in vitiligo patients. The mechanism of action of NB-UVB in vitiligo is through induction of local immunosuppression and stimulation of the proliferation of melanocytes in the skin and the outer root sheath of hair follicles. There is a stimulatory effect on melanogenesis and on the production of Melanocyte Stimulating Hormone (MSH). Comparison studies have shown a significantly enhanced rate of repigmentation with NB-UVB compared with topical Psoralen and Ultraviolet A (PUVA) therapy[10]. Furthermore, the incidence of adverse effects seen commonly with topical PUVA, such as phototoxicity, is significantly reduced with the use of NB-UVB.

NB-UVB has shown a number of advantages over PUVA in vitiligo patients in addition to its excellent efficacy. These advantages include its extremely low side-effect profile particularly on the systemic front, its established safety in children, and safety in pregnant females. NB-UVB also has considerably better patient compliance as there is no need to time the exposure with any drug intake or any need for eye protection beyond treatment exposure time. A recent double-blind randomized study comparing NB-UVB with PUVA demonstrated a much better efficacy with NB-UVB. The study found that repigmentation achieved with NB-UVB was much better with respect to colour matching with uninvolved skin, and this was also more persistent than that achieved with PUVA[11].

In addition NB-UVB has been used in childhood vitiligo with excellent results[12]. No additional adverse effects were seen in children with NB-UVB as compared with those in adults. NB-UVB is now preferred over all other treatment options in the management of generalized vitiligo in both adults and children[13].

NB-UVB has been used in combination with different topical agents to increase its efficacy and thus shorten the total duration of treatment. Treatment options that have been used with NB-UVB in vitiligo till date include topical tacrolimus,[14,15] pimecrolimus,[16] Vitamin D analogues[17,18] and even topical pseudocatalase[19]. While some studies have shown a synergistic effect with these combinations, others have found the efficacy of the combinations to be similar to NB-UVB alone. In one half-body comparison study, topical placental extract was used in combination with NB-UVB but the combination was shown to offer no added benefit than NB-UVB alone[20]. Therefore, the ideal topical agent to be combined with NB-UVB remains unknown.

Laser Therapy

Excimer laser, which uses Xenon-Chlorine (Xe-Cl) gas and produces a monochromatic laser light of 308 nm wavelength, is another innovative treatment option for vitiligo. The laser system has been used with increasing frequency over the last few years for targeted treatment of individual vitiligo lesions[21]. The laser is used either alone or in combination with topical immunomodulator or PUVA-sol therapy[22,23]. Treatment with this laser is claimed to give extremely good and early results in both localized and segmental vitiligo. Repigmentation was found to be better on the face and trunk than on the extremities[24].

Topical therapies, particularly topical tacrolimus, have been used in combination with Excimer laser. This combination has been claimed to be more effective than Excimer laser alone. In a randomized right-left comparison study with 14 patients, Excimer light monotherapy was compared with a combination of Excimer laser with topical tacrolimus. While 20% of lesions treated with Excimer laser alone achieved >75% repigmentation, the same degree of repigmentation was obtained in 70% lesions with the combination treatment[22]. Topical methoxsalen has also been used in combination with Excimer laser phototherapy and this has been claimed to have worked better than laser therapy alone[23].

Targeted UVB therapy

This is another recent innovation in vitiligo management that has arrived over the last few years. The beauty with this therapy is that it delivers high intensity UVB light only to the affected vitiliginous areas, avoiding any exposure to the uninvolved skin. This not only decreases the cumulative UVB dose received by an individual patient, but is also claimed to improve the efficacy of treatment quite significantly.

Targeted UVB therapy, as expected, finds its use more in the treatment of focal and segmental types of vitiligo. In fact, the first study with targeted UVB therapy was done on eight patients with segmental vitiligo. Five of these patients achieved >75% repigmentation of their lesions with this therapy[25].

Targeted UVB therapy offers certain advantages over Excimer laser phototherapy. The treatment is safer and more efficacious compared with conventional UVB therapy, and almost as efficacious but much less costly than Excimer laser therapy[26].

Systemic immunomodulator therapy

Vitiligo is thought to be an immune-mediated disease and thus immunosuppressive and immunomodulator agents have been used on a regular basis in this disease. Among the immunosuppressant, systemic steroids have been the most commonly used. However, systemic steroid therapy has always been associated with a high incidence of adverse effects especially in children which is the age-group most commonly affected. To overcome this limitation, steroids have been given in pulse or even in mini-pulse form.

A prospective study involving 14 patients with progressive or static vitiligo showed cessation of disease activity and a repigmentation rate of 10- 60% after high-dose methylprednisolone pulse therapy administered on three consecutive days[27]. Systemic steroids have also been administered in a mini-pulse form on two consecutive days every week, known as Oral Minipulse (OMP) therapy. The first study demonstrating the efficacy of OMP with oral betamethasone (0.1mg/kg with a maximum of 5mg) was described in 1991[28]. In a later study on childhood vitiligo, betamethasone was replaced by oral methylprednisolone and combined with topical fluticasone ointment on the vitiligo lesions. The disease was arrested in >90% of patients, and >65% of children achieved good to excellent (>50%) repigmentation of their vitiligo lesions[29].

Topical Vitamin D analogues

Vitamin D analogues, particularly Calcipotriol, have been used topically either alone or in combination with topical steroids in the management of vitiligo. The basis for the use of these agents is that Vitamin D3 affects the growth and differentiation of both melanocytes and keratinocytes. This has been further proved by the demonstration of receptors for 1 alpha-dihydroxyvitamin D3 on the melanocytes. These receptors are believed to have a role in stimulating melanogenesis[29]. Vitamin D analogues have given variable results in the treatment of vitiligo in different studies. These agents have also been used in combination with UV-light (including NB-UVB) and topical steroids with variable results[30-32].

Topical immunomodulators

Topical immunomodulators, such as tacrolimus and pimecrolimus, have been the most promising recent additions to topical vitiligo therapy. In fact because of their efficacy and a remarkable safety profile the use of these agents in vitiligo has shown a consistently increasing trend over the last few years. These agents can be safely administered in young children, as they don't cause any atrophy or telangiectasia of the skin even after prolonged use. There is also no risk of hypothalamic-pituitary-adrenal (HPA) axis suppression as seen with the widespread use of potent topical steroids[33]. The first study that demonstrated the efficacy of tacrolimus in vitiligo was published in 2002. In this study tacrolimus was used in six patients with generalized vitiligo and five of them achieved >50% repigmentation of their lesions by the end of study period. Since then many additional studies have been published on this subject and have clearly demonstrated the role of topical tacrolimus in vitiligo. The best results with topical immunomodulator therapy have been seen on exposed parts of the body such as the face and neck and, as with any other therapy, the acral parts of the body respond the least[34,35]. Similar results were obtained with the use of topical pimecrolimus in vitiligo patients[36].

Pseudocatalase

Pseudocatalase has been used in combination with Dead Sea climatotherapy or UVB exposure for the treatment of vitiligo. The basis for the use of this agent in vitiligo is the evidence of oxidative stress and high H_2O_2 levels in the lesional skin[37]. While some earlier studies demonstrated excellent results with this agent in inducing repigmentation in vitiligo, later studies have cast doubts on its efficacy[38]. Pseudocatalase is used topically on the lesional skin, and this is followed by UVB exposure to the whole body or to the lesional skin. The combination is claimed to correct the oxidative stress on melanocytes in vitiligo patients and thus lead to correction of the depigmentation.

Topical 5-Fluorouracil

Topical 5-fluorouracil is supposed to induce repigmentation of vitiligo lesions by overstimulation of follicular melanocytes which migrate to the epidermis during epithelialization[39]. This form of topical therapy can be combined with spot dermabrasion of the vitiligo lesions to improve the repigmentation response. In a study by Sethi et al, a response rate of 73.3% was observed with a combination of spot dermabrasion and topical 5-fluorouracil after a treatment period of six months[40].

Surgical therapies

Surgical therapies for vitiligo have further increased the percentage cure of the disease by an appreciable degree, with the consequent increase of their use in the management of unresponsive vitiligo. These surgical therapies, as a rule, are indicated in those patients who have a stable (non-progressive) disease of at least one year and not responding to medical treatment. In general the most important advantage with these procedures is that the chances of repigmentation of lesions are in the range of 90-100%. Moreover, these interventions are becoming better and easier to perform with every passing day.

Different surgical therapies that have been attempted in the management of vitiligo include autologous suction blister grafting, split-thickness grafting, punch grafting, smash grafting, single follicular unit grafting, cultured epidermal suspensions and autologous melanocyte culture grafting. All these grafting procedures, except the melanocyte culture grafting, are easy to perform and do not require any sophisticated instruments. These grafting techniques have now been divided into two types, tissue grafts and cellular grafts, depending on whether whole epidermal/dermal tissue is transplanted or the individual cellular compartment.

Tissue grafting technique

Suction blister grafting

Here, thin epidermal grafts are taken from suction blisters on the donor site, usually on the buttocks or thighs. These suction blisters are produced by applying sufficient negative pressure on the skin at the donor site by using a suction apparatus or syringes with three-way cannulae. The epidermal grafts are then transplanted on to dermabraded vitiligo lesions. This leads to repigmentation of the recipient areas with an excellent cosmetic matching. The ease of the procedure, the high success rate and the excellent cosmetic results have all made suction blister grafting the procedure of choice in vitiligo grafting[41].

Split thickness grafting

In this grafting technique a thin split thickness graft is taken from a donor site with the help of a dermatome, Humby's knife, Silver's knife or a simple shaving blade. This graft is then transplanted on to dermabraded recipient areas. This technique also gives excellent cosmetic matching after repigmentation and the incidence of repigmentation in this technique is also quite high. In fact, most comparison studies on grafting techniques in vitiligo have shown that maximum repigmentation is achieved with either suction blister grafting or split thickness grafting[41]. The advantage of partial thickness grafting over the suction blister method is that a relatively larger area of vitiligo can be tackled in a single sitting. Both partial thickness skin grafting as well as suction blister grafting can be followed up by NB-UVB to achieve faster and better results.

Miniature punch grafting

Here full-thickness punch grafts of 1.0 to 2.0 mm diameter are taken from a suitable donor site and then transplanted on to similar punch shaped beds on the recipient vitiligo lesions. The recipient area is then treated with either PUVA/PUVA-sol or topical steroids leading to spread of pigment from the transplanted punches to the surrounding skin. With time the whole of the recipient area gets repigmented. The advantages of this procedure are that it is easy to perform and can take care of a relatively larger vitiligo area compared with the above two procedures. Also vitiligo lesions with irregular or geographical shapes can be treated with this procedure. However there are certain limitations. There is the risk of 'cobblestone appearance', 'polka-dot appearance', and hypertrophic changes at the recipient site[42]. All these side effects can be minimized by proper patient selection and by use of smaller sized punches of 1.0 to 1.5 mm diameter. Miniature punch grafting is presently the commonest surgical procedure performed in India on vitiligo patients.

Follicular unit grafting

In this technique, single-hair follicular units are harvested/prepared from a suitable donor area as in the case of hair transplantation. These follicular units are then cut above the level of the follicular bulb and then transplanted into vitiligo lesions. The idea behind this technique is that the melanocytes in the follicular unit are 'donated' to the vitiliginous skin and serve as a source of pigment at the recipient site. The repigmentation process here simulates the normal process of repigmentation of vitiliginous skin quite closely and thus gives an excellent cosmetic result. This procedure combines the advantages of punch grafting with the excellent cosmetic results of split thickness or blister grafting techniques[43]. The procedure is however tedious and needs good expertise on the part of the cosmetic surgeon.

Smash grafting

In this technique, a partial thickness graft is taken and is 'smashed', or cut into very small pieces, by means of a surgical blade on a suitable surface such as a glass slide. This 'smashed' tissue is then transplanted on to the dermabraded recipient skin and covered with a special powder or corrugated tube dressing so as to keep the smash-graft undisturbed on the recipient area. The advantage of this technique, over a simple partial thickness grafting, is that thicker grafts can be used with a good cosmetic result. The procedure has been indicated for those who are relatively inexperienced and cannot take an ideal, thin and transparent partial thickness graft from the donor area[44].

Cellular grafting techniques

Non-cultured epidermal suspensions

Here a split-thickness graft is taken from a donor area and then incubated overnight. On the next day the cells are mechanically separated using trypsin-EDTA

solution and then centrifuged to prepare a suspension. This cell suspension is then applied to the dermabraded vitiligo lesions, and a collagen dressing is applied to keep it in place. A relatively large area of vitiligo, about ten times the size of the donor graft can be taken care of with this procedure[45]. The recipient area however has to be treated with either NB-UVB or PUVA for two to three months to achieve the desired pigmentation.

Melanocyte culture transplantation

This is a relatively more advanced grafting procedure where, once again, a split-thickness graft is taken from a donor area and incubated in an appropriate culture medium to grow the melanocytes or the keratinocytes-melanocyte combination in vitro. The cultured cells are then applied onto laser dermabraded, or even mechanically abraded, lesional skin[46,47]. The procedure is obviously more difficult to perform, as it needs the advanced laboratory facilities for melanocyte culture. However the results with this procedure are excellent and a relatively large area of involved skin can be tackled by a single donor graft.

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