



Current remedies for vitiligo

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ABSTRACT

Vitiligo is a disorder with complex causes and is a type of autoimmune disease in which the immune system targets the body's own pigment cells and tissues. Our aim is to present an overall view of the current remedies widely adopted for the treatment of vitiligo. Medical treatments target the immune system, and try to reverse the destruction. The goal is to restore the skin's color by restoring healthy melanocytes to the affected area. Apart from melanocytes, vitiligo autoantigens appear also on other cells. Even though antibodies to pigment cells are not an agent of vitiligo, the most valuable contribution is that anti-melanocyte antibody reactivity can help in identifying relevant antigens. T cells from vitiligo skin are highly reactive towards melanoma cells and serve as an effective source to treat melanoma and stays as a solution for vitiligo. There have been many treatments to cure vitiligo such as use of steroid creams, PUVA (psoralen and ultraviolet A light), narrow band UVB (ultraviolet B), various surgical techniques, vitamin D analogues and pseudocatalase. These treatments are subjected for undesired side effects whereas some herbal and natural treatments act against the immune system with no side effects.

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1. Introduction

Vitiligo (leukoderma) is a pigmentation disorder in which melanocytes, the cells that make pigment which give color to the skin, are destroyed. This results in smooth, white patches in the midst of normally pigmented skin. The term vitiligo is probably derived from the Latin word *Vitilus* – meaning calf and was first named by Roman physician Celsus of first century AD. People with vitiligo may also have eye abnormalities and have a higher incidence of thyroid disease, diabetes mellitus, and pernicious anemia. 1–2% of the world's population seeks treatment for this autoimmune disorder. White patches appear on the skin in different parts of the body. Similar patches also appear on both the mucous membranes (tissues that line the inside of the mouth and nose), and the retina (inner layer of the eyeball). The hair that grows on areas affected by vitiligo sometimes turns white. It can begin at any age but in about 50% it starts before the age of 20 [1].

1.1. Factors which can cause vitiligo

Vitiligo is a disorder with complex causes. The emergence of white patches can be brought on by a variety of impinging causes. Many people report that their vitiligo first appeared following a stressful event, such as an accident, job loss, death of a family member, severe sunburn, or serious illness [2]. There are mainly three theories about the underlying mechanism of vitiligo. One theory states that nerve endings in the skin release a chemical that is toxic to the melanocytes. A second theory states that the melanocytes simply self-destruct. The third theory is that vitiligo is a type of autoimmune disease in which the immune system targets the body's own cells and tissues.

1.2. Autoantibody responses

Antibodies to melanocytes are in the blood of patients with vitiligo. These antibodies are related to the extent of the disease being detected in 50% of patients with minimal vitiligo compared with 93% of patients with greater depigmentation. Immunofluorescence has detected that the binding of vitiligo patient IgG to cultured melanocytes increased with disease extent and activity. Some vitiligo autoantigens appear to be expressed on cells other than melanocytes, including the MCHR1. The most valuable contribution is that studies on anti-melanocyte antibody reactivity can make help in identifying relevant target antigens [3].

2. Treatments

2.1. Autoimmune vitiligo T cells

The skin is made up of keratinocytes and melanocytes. The keratinocytes make up the bulk of the skin. The melanocytes are the cells that make the skin color. In people with vitiligo, the immune cells which fight infection, attack the melanocytes and damage them [2]. When the melanocytes in a certain area die, the skin turns white. Vitiligo sometimes runs in families, meaning that a genetic factor may be involved. Vitiligo sometimes occurs at the site of an old injury. Even though the condition cannot be cured drastically, medical treatments target the immune system, and try to reverse the destruction [4]. The

goal is to restore the skin's color by restoring healthy melanocytes to the skin (repigmentation) allowing the skin to regain its normal appearance [5]. T cells are more common in vitiligo skin and remains in lesional area but most of the infiltrate appears to migrate with the depigmenting epidermal border. The infiltrate consists not only of CD8 but also of CD4 T cells. Skin infiltrating T cells can be isolated and propagated without antigen selection in the presence of IL-2 and anti-CD3/anti-CD28 antibody coated beads. T cells have been isolated from perilesional skin of a vitiligo patient. These T cells were found to have similar reactivity towards vitiligo patient melanocytes. Autoimmune response may be allowed to grow and develop in the absence of functional T regulatory cells. These cells actively mediate suppression of the immune system generally by secreting IL-10 and TGF- β to prevent autoimmunity. Polyclonal cytotoxic T cells derived from vitiligo skin are highly reactive towards melanoma cells and may serve as a superior source of high affinity TCR genes to treat melanoma [6].

2.2. Steroids

Steroid creams are the first line of treatment. They are usually applied twice daily, and results require three to six months. Side effects are observed when overdosed, which include local skin damage, and glaucoma or cataracts when used around the eyes [7]. Regular monitoring and adjusting the potency of the creams to be appropriate for the location can avoid these side effects.

2.3. PUVA

For extensive vitiligo, oral medications of psoralen and phototherapy by ultra violet rays (PUVA) can be tried. It takes at least 2–3 months or about 200 treatment sessions required to have an effect. PUVA is partially successful in those treated, but complete repigmentation occurs in only 15–20%. Repigmentation occurs slowly as the cells creep back in over months to years.

2.4. Water bath PUVA

The most recent model in phototherapy is water bath PUVA, in which the patient lies in a bath tub containing psoralen water for 15 min so that the drug gets absorbed on the skin and then goes for light therapy. This kind of therapy is especially beneficial in children for whom oral medicines are not safe [8]. Another method of psoralen treatment, used rarely for pediatric patients with small, scattered vitiligo patches, involves the application of a very dilute solution of the drug directly to the affected skin area. This is then exposed to sunlight. Such topical treatment makes a person very liable to severe burn and blisters following too much sun exposure whereas water bath PUVA has the advantages of being done at home, and does not damage the entire skin surface.

2.5. Narrow band UVB therapy

Narrow band UVB therapy or TL-01 therapy is the latest in phototherapy for the treatment of vitiligo. In this therapy there is no need to take oral psoralen or apply psoralen. The therapy is very safe and can be safely administered even to children. Narrow band UVB

light is at a wavelength of 311 nm. Narrow band UVB is much safer than full spectrum UVB. Narrow band UVB is the faithful wavelength that vitiligo responds to best [9]. It's a fact that if exposure to natural sunlight is equal to 100% UV radiation exposure, using a narrow band UV light is roughly 1% UV radiation exposure.

2.6. Tissue grafts

The grafts will be implanted into perforations made at the recipient site using a biopsy punch under local anaesthesia. The grafts should be placed 4–8 mm apart because apparently pigment cells seem not to migrate beyond 5 mm. The grafted area will then be covered with petrolatum gauze or a transparent adhesive tape and secured with bandages to give compression and fixation for at least one week. The success rate of this technique depends upon the individual skin type [10–12]. Difficult areas like lips can also be treated using this technique. Repigmentation is based on the pigment spread phenomena by the grafted piece of normal skin. Pigment spread occurs gradually after grafting within 1 month and full repigmentation can be achieved in 3–6 months [13].

2.7. Split thickness skin grafts

This technique has a high success rate of 78–91%. After obtaining a split thickness skin graft using a dermatome it can be applied directly to the derma braded recipient area. Temporary small epithelial milia like cysts can be observed in the recipient area during the first months, especially on the face and neck. Scar or keloid formation at the donor site is reported in 12% of the patients treated with split thickness grafts. As donor tissue is limited more than one split skin grafting session can be necessary [14].

2.8. Suction blister grafts

Grafts are carefully removed with sharp scissors and forceps after harvesting the graft. This epidermal sheet is then grafted onto the denuded recipient site. The success rate is 73–88%. Pigment spread after epidermal blister grafting can be enhanced by pre operative radiation therapy of the donor site using PUVA. Temporary hyper pigmentation can be seen in the grafted sites in 2–65% [14].

2.9. Non cultured keratinocytes and melanocytes

Transplantation technique with a suspension of non cultured keratinocytes and melanocytes in the treatment of depigmented lesions is effective. Donor skin is obtained from the occipital area and immersed for 18 h in 0.25% trypsin solution. The following day the epidermis of the donor skin can be separated from the dermis *in vitro* using fine forceps. After several procedures a cellular suspension is obtained [15]. Liquid nitrogen is used to induce blisters in the recipient area. The cellular suspension from the donor site is injected into each blister at the recipient area after aspiration of the viscous blister fluid. The intact blister top is a natural dressing that holds the transplanted cells in place. It is important not to separate keratinocytes from melanocytes before grafting because factors furnished by keratinocytes sustain melanocyte growth [14].

2.10. Transplantation of cultured melanocytes

Lerner et al., first described the use of cultured pure autologous human melanocytes. They explained pigment cells of a shave biopsy from normally pigmented skin *in vitro* with the addition of several growth factors and chemical media [16].

2.11. Cultured epidermal grafts

A shave biopsy of normally pigmented skin is the source for epidermal cell culture. After separating the epidermis from the dermis the cells are seeded in a medium that allows co-cultivation of melanocytes and keratinocytes. After a week a cultured sheet is obtained, released by treatment with dispase and attached to petrolatum gauze as support. Subsequently the gauze to which the epithelium adheres will be applied onto the derma braded recipient site and covered with occlusive dressing [17]. The greatest advantage of this technique is the potential expansion of the cells in culture, which permits treatment of a wide area of hypomelanosis with a small sacrifice donor skin. Because only superficial derm abrasion is performed, the procedure is non scarring [17].

2.12. Stability in surgical repigmentation of vitiligo

Even after almost thirty years of implementing surgery in vitiligo, there seems to be little consensus among workers regarding the optimal required period of stability. After several years of experience in surgical repigmentation of vitiligo, some interesting observations are raising up. The observation is that even after grafting, the pigment spread from successive sessions of grafting can be unpredictable; perigraft spread of pigment may be minimal or absent and in some cases even depigmentation of grafts is noted [18].

2.13. Autologous skin grafts

This type of skin grafting is often used for patients with small, stable patches of vitiligo (recipient sites). Normal unaffected skins from the thigh or buttocks area of a patient's body (donor sites) were taken and fixed it to an area of vitiligo. The treated area responds almost 90% of the time, but may develop a cobblestone appearance, or a spotty pigmentation, or may fail to re-pigment at all [19].

2.14. Fake tanning products

Cover creams or self tanning products are special drug cosmetics that can be used to match most skin patches when medical treatment is not successful. All patients with vitiligo should always protect their depigmented skin against excessive sun exposure by wearing protective clothing. Tattooing is rarely recommended. It works best for the lip area, particularly in people with dark skin. However, it is difficult to perfectly match the skin, and tends to look worse over time. The remaining skin will be an even white color, which can then be covered with the cosmetics. Cosmetics can be used to improve the appearance of the white areas not covered by clothing. Sunscreens give coolness to the affected areas and also prevent the normal skin around the patches from becoming darker. Bleaching or depigmentation of the normal skin and autologous transplantation of skin are an option for those who are severely affected [20].

2.15. Vitamin D analogues

Combination of PUVA (psoralen-sun therapy) and calcipotriol is highly effective and may be used for shortening the therapy with PUVA in the treatment of patchy areas of vitiligo depigmentation [21]. Topical calcipotriol appeared to be an effective and well tolerated treatment for vitiligo and it can be safely used in conjunction with PUVA [22].

2.16. Pseudocatalase

It has been shown that patients with vitiligo have an extremely low catalase activity [22]. Topical application of pseudocatalase (a low molecular weight inorganic complex of unknown formula with

catalase activity) used in combination with short term UVB light exposure has been reported in an open study to show repigmentation. Complete repigmentation on the face and dorsum of the hands appeared in 90% of those treated [22].

2.17. Herbal products

2.17.1. Anti-vitiligo® (True Herbals, Lahore, Pakistan)

Anti-vitiligo® (True Herbals, Lahore, Pakistan) is a traditional herbal formulation which was available internationally since November 2003. It is effective both in disease of recent onset as well as long standing established cases. Formulation contains the following ingredients.

2.17.2. *Psoralea corylifolia*

It is a rich source of naturally occurring psoralen. It sensitizes human skin to the tanning effect of UV and sun light. *P. corylifolia* has been traditionally used both orally as well as in the form of topical preparations. Oxidative stress is widely believed to be one of the likely causative factors in the initiation of white skin patches of vitiligo. Hence, the protective, anti-oxidative and anti stress properties of *P. corylifolia* may contribute to the improvement in the hypo-pigmented white skin patches of vitiligo.

2.17.3. Black cumin

Seeds of *Nigella sativa* have also been having an immunomodulatory as well as anti cancer effect, which is due to augmentation of T cell and natural killer cell mediated immune responses [23].

2.17.4. Barberry root

Barberry root or the root of *Berberis vulgaris* contains numerous chemicals and bioactive compounds of medical significance. It contains for example the alkaloids like berbamine, berberine, and oxyacanthine. Other compounds include tannins, chelidonic acid and resins. It is also quite rich in B-vitamin thiamine, lutein, vitamin C, beta-carotene, zeaxanthin, zinc, chromium, and cobalt. This herb has also been shown in scientific studies to possess antioxidant and cytoprotective properties [23].

2.17.5. Kalawalla® (American Life Style, New York, USA)

Kalawalla® (American Life Style, New York, USA) is a herbal product that works as a natural immunomodulator with proven immunomodulating effect. The product contains *Polypodium leucotomos* standardized extracts. *P. leucotomos* is a fern plant extract that has been used in Europe to treat vitiligo for over 10 years with encouraging results. Vitiligo is characterized by skin depigmentation and is commonly associated with the immune system. The extract can help to regulate the immune system bringing it to its healthiest, strongest and balanced levels. Repigmentation results can be seen within the first month of taking the product. *P. leucotomos* standardized extract has been known to increase the lymphocyte levels. It is also known to regulate the CD4/CD8 ratios to their normal values [24]. This product contains (per capsule): *P. leucotomos* extract 120 mg and *P. leucotomos* rhizome 280 mg.

2.18. Piperine

The synthetic derivatives of piperine can stimulate pigmentation in the skin especially when combined with UVR treatment [25]. The studies have compared the effects of piperine and its analogues tetrahydropiperine (THP), cyclohexyl analogue of piperine (CHP) and reduced CHP (rCHP) when applied to the skin of mice, either alone or followed by UV treatment. CHP did not show significant results while piperine, THP and rCHP did induce pigmentation in the skin. When used alone, the compounds stimulated pigmentation to an even, light brown color within six weeks. However, by accompanying the use of

piperine or THP with UV, the skin became significantly darker, and within only seven weeks as compared to other treatments which take a year or so [25].

3. Discussions

Vitiligo is an autoimmune disease which targets pigment cells and constitutes a huge research innovation for those interested in melanocyte biology and pigmentation disorder. Topical steroids are probably first line therapy for most patients. There are a number of other therapies such as surgical techniques that seem promising. However, further studies are necessary. But now the time has come to offer patients hope for therapy by identifying suitable antibody targets in vitiligo. T cells from vitiligo skin are highly reactive towards melanoma cells and serve as an effective source to treat melanoma. This could also provide a basis for the development of diagnostic tests. Antigens recognized by vitiligo antibodies could serve as markers for important T cell responses in patients with the disease.

4. Take-home messages

- Steroid creams are the first line treatment for vitiligo.
- Oral medications of psoralen and phototherapy by ultra violet rays (PUVA) can be tried for extensive vitiligo.
- Combination of PUVA (psoralen-sun therapy) and calcipotriol is highly effective.
- Black cumin has an immuno-modulatory effect due to augmentation of T cell and natural killer cell mediated immune responses.
- *P. leucotomos* is a fern plant whose extract has been used in Europe to treat vitiligo for over 10 years with encouraging results.
- Piperine can stimulate pigmentation in the skin especially when combined with UV treatment.

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Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients: a randomized double-blind controlled study

Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients is still an interest are for discussion. **Konai MS, et al. (*Clin Exp Rheumatol* 2009;27:214–21)** intended to compare the efficacy and safety of intraarticular glucocorticoid injection to its systemic use for treatment of knee synovitis in rheumatoid patients. A randomized double-blind controlled study was conducted including 60 patients with RA. Patients were randomized to receive either a single intraarticular knee injection with triamcinolone hexacetonide 60 mg (3 ml) and xylocaine chloride 2% (1 ml) associated to a single intramuscular injection of 1 ml of xylocaine chloride 2% (IAI group) or 1 ml of xylocaine chloride 2% by intraarticular injection and a intramuscular injection of triamcinolone acetone 60 mg (3 ml) and xylocaine chloride 2% (1 ml) (IM group). All patients were blindfolded for the procedure. Evaluations were performed at baseline and 1, 4, 8 and 12 weeks post-intervention. The following instruments were used: VAS for knee pain, as primary outcome, VAS for knee morning stiffness and edema; the ACR 20, 50 and 70% improvement criteria; knee circumference and goniometry; Likert's scale of improvement; daily use of oral glucocorticoid and NSAIDs, blood pressure and adverse effects. The researchers found that patients in the IAI group had significantly better results for VAS for knee pain, edema and morning stiffness as well as for improvement evaluation after intervention according to the patient ($p < 0.001$) and physician ($p = 0.02$). The results demonstrate that intraarticular injection with glucocorticoids is superior to its systemic use for the management of monoarticular synovitis in rheumatoid patients. The intraarticular approach showed better results in terms of local inflammatory variables and improvement evaluation by the patient and physician.

Macrophage activation syndrome in juvenile systemic lupus erythematosus: A multinational -multicenter study of thirty-eight patients

To describe the clinical and laboratory features of macrophage activation syndrome as a complication of juvenile systemic lupus erythematosus (SLE) **Parodi A, et al. (*Arthritis Rheum* 2009;60:3388–3399.)** performed a study including cases of juvenile SLE-associated macrophage activation syndrome belonging to 3 pediatric rheumatology networks. Patients who had evidence of macrophage hemophagocytosis on bone marrow aspiration were considered to have definite macrophage activation syndrome, and those who did not have such evidence were considered to have probable macrophage activation syndrome. Clinical and laboratory findings in patients with macrophage activation syndrome were contrasted with those of 2 control groups composed of patients with active juvenile SLE without macrophage activation syndrome. The ability of each feature to discriminate macrophage activation syndrome from active disease was evaluated by calculating sensitivity, specificity, and area under the receiver operating characteristic curve. The study included 38 patients (20 with definite macrophage activation syndrome and 18 with probable macrophage activation syndrome). Patients with definite and probable macrophage activation syndrome were comparable with regard to all clinical and laboratory features of the syndrome, except for a greater frequency of lymphadenopathy, leukopenia, and thrombocytopenia in patients with definite macrophage activation syndrome. Overall, clinical features had better specificity than sensitivity, except for fever, which was highly sensitive but had low specificity. Among laboratory features, the best sensitivity and specificity was achieved using hyperferritinemia, followed by increased levels of lactate dehydrogenase, hypertriglyceridemia, and hypofibrinogenemia. Based on the results of statistical analysis, preliminary diagnostic guidelines for macrophage activation syndrome in juvenile SLE were developed. The authors' findings indicate that the occurrence of unexplained fever and cytopenia, when associated with hyperferritinemia, in a patient with juvenile SLE should raise the suspicion of macrophage activation syndrome. They propose preliminary guidelines for this syndrome in juvenile SLE to facilitate timely diagnosis and correct classification of patients.

Epigenetics in multiple sclerosis susceptibility: difference in transgenerational risk localizes to the major histocompatibility complex

Major histocompatibility complex has been shown to play a weighty role in the susceptibility to develop Multiple sclerosis (MS), especially when certain haplotypes contain the HLA-DRB1*1501 allele. However, some interesting epidemiological evidence has demonstrated that epigenetic factors might cause distortion in the transmission of the disease in aunt/uncle-niece/nephew (AUNN) pairs. That means that the frequency for the HLA-DRB1*1501 allele is different between the first and second generations of people affected by MS, suggesting that there are other epigenetic factors influencing such risk. A recent study performed by **Chao MJ, Et al. (*Hum Mol Genet.* 2009;18:261–6)** showed that the HLA-DRB1*1501 allele frequencies were significant different between the first and second generations affected. Affected aunts had significantly lower HLA-DRB1*15 frequency compared with their affected nieces (Chi-square = 9.90, $P = 0.0016$), whereas the HLA-DRB1*15 frequency in affected males remains unaltered across the two generations (Chi-square = 0.23, $P = 0.63$). After compared transmissions for the HLA-DRB1*15 allele using a family-based transmission disequilibrium test approach in 1690 individuals from 350 affected sibling pair (ASP) families and 960 individuals from 187 AUNN families; they found that transmissions differed between the ASP and the AUNN families (Chi-square = 6.92; $P = 0.0085$). The risk carried by HLA-DRB1*15 was increased in families with affected second-degree relatives (AUNN: OR = 4.07) when compared with those consisting only first-degree relatives (ASP: OR = 2.17), establishing heterogeneity of risk among HLA-DRB1*15 haplotypes based on whether collateral parental relatives are affected. Such findings can be understood as the product of gene-environment interactions among other unknown likely genetic interactions. These data also strongly suggest that the female-specific increasing risk of MS is mediated through these alleles or adjacent variation. The comparison of transmission of the same allele in vertically affected pedigrees (AUNN) to collinear sibling pairs (ASP) may provide a useful screen for putative epigenetic marks.