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Different Modalities For Treatment Of Vitiligo

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Abstract
Background: Vitiligo is a prevalent acquired disorder of pigmentation, affecting individuals globally. Numerous therapeutic modalities had been recommended for vitiligo such as phototherapy, topical and systemic corticosteroids, calcineurin inhibitors, vitamin D3 analogue derivatives, 5-flurouracil, laser therapy, and surgical techniques. However, there is no treatment to ensure complete cure of vitiligo, therefore, combination therapy is frequently recommended. **Objectives**: This article aims to review different modalities in treatment of vitiligo. **Conclusions**: Vitiligo treatment can sometimes be frustrating due to the inconsistency in clinical improvement and its relapsing feature. Therapy should be individualized according to the type of vitiligo, presence of activity and the side-effect profile of the drug used.

Key words: Vitiligo,melanocyte,NB-UVB and fractional CO2 laser therapy

1. Introduction

Vitiligo is an acquired pigmentary disorder that manifests itself globally. Its prevalence ranges from 0.5 to 2 percent across all demographics, including age, race, gender, ethnicity, and skin color (1). Vitiligo is characterized by the death of functional melanocytes in the skin.Many competing hypotheses on what causes melanocytes to stop working are still up for debate, and the precise pathophysiology remains unknown. There are a lot of hypothesized pathophysiological mechanisms, including oxidative stress, autoimmune, heredity, and dysfunction of the neurological system (2). The dermatological therapy of vitiligo remains a formidable obstacle. An assortment of topical medicines, including corticosteroids, calcineurin inhibitors, vitamin D analogues, phototherapy, systemic steroids, antioxidants, and surgical treatment, have been explored as potential vitiligo treatments. Lesions on the face, neck, or trunk, as well as younger patients, darker skin types, and those whose illness has only recently manifested, tend to have the best treatment responses. Although segmental vitiligo is not progressing, it is rarely treated properly. A familial history of vitiligo, mucosal involvement (often acral lesions), and treatment resistance are all factors in the development and progression of the illness. Because patients often undergo psychological stress as a result of lengthy treatment durations and emotions of frustration resulting from prior treatment failures, psychotherapy serves an important purpose in alleviating this condition (3). Unfortunately, vitiligo cannot be cured entirely with any therapy. (4) In vitiligo, the process of re-pigmentation uses melanocytes that are either already present in the surrounding pigmented skin or in the outer root sheath of hair follicles. 5. One adjuvant threptic alternative for stable vitiligo is the fractional carbon dioxide (CO2) laser. Its goal is to enhance the skin penetration of medicinal ingredients and activate melanocytes. It creates tiny treatment zones by coagulating necrotic columns rather than ablating the whole epidermis. the sixth

2. Vitiligo

In vitiligo, a chronic acquired pigmentation condition, white macules appear on the skin as a result of many causes that trigger the death of epidermal melanocytes (7).

What causes vitiligo?

The characteristic feature of vitiligo is the deterioration of functional melanocytes in the skin.Many competing hypotheses on what causes melanocytes to stop working are still up for debate, and the specific pathophysiology and etiology remain unknown. There are a lot of hypothesized pathophysiological mechanisms, including oxidative stress, autoimmune, heredity, and dysfunction of the neurological system. eight (8)

1. The hypothesis of genes

Because of the wide range of possible causes and manifestations of vitiligo symptoms, as well as the fact that the disease can manifest at any age and in a variety of ways, genetic epidemiological research has established that this condition is best understood as a complex hereditary disorder. Complex hereditary disorders are often oligogenic or even polygenic, meaning that each gene adds to the relative risk to some extent; Through the use of the vitiligo phenotype in linkage analysis, genes on chromosomes 1, 4, 6, 7, 8, 17, and 22 were identified as having a susceptibility to the condition.the ninth

Theory of the immune system part two

It is possible for vitiligo to be passed down over many generations of a family in a partially penetrant autosomal dominant

pattern. A hereditary predisposition to vitiligo is higher in families where autoimmune disorders are present. Vitiligo is associated with autoimmune diseases, including as SLE and autoimmune thyroid disorders. in ten

3. The hypothesis of oxidative stress

Evidence that some of the byproducts of melanin production, such dopaquinones and indoles, are toxic to melanocytes lends credence to this idea. Vitiligo patients run the risk of systemic oxidative damage due to an insufficiency in their antioxidant defenses, which include both enzymes and non-enzymatic components. Low glutathione peroxidase and decreased glutathione levels may cause oxidative stress in non-segmental vitiligo, but low catalase levels may contribute to oxidative stress in segmental vitiligo. (11)

Theory of neurochemistry, fourth

The symmetrical appearance of vitiligo lesions suggests a possible involvement of the neurological system. Also, there's a lot of evidence that shows how mental stress may worsen or even develop vitiligo. Melanocytes are sensitive to the neurotransmitters acetylcholine (Ach) and norepinephrine (NE). Melano cytotoxicity is caused directly by NE because it inhibits melanogenesis, limits mitochondrial calcium uptake, and disrupts cellular sulfhydryl groups. (12)

5. The melanocytorrhagy hypothesis, often known as the adhesion defect theory

Some have hypothesized that aberrant adhesions are to blame for the melanocyte loss seen in vitiligo lesions. Up to 31% of Caucasian people with common vitiligo may exhibit koebnerization, which is also called the Köebner phenomenon. This is the principal clinical indication that supports this idea. Even little skin damage may raise basal melanocyte tyrosinase activity, decrease melanin transfer to keratinocytes (KCS), and detach some melanocytes. (13)

6. The idea of biochemistry

Deregulation of biopterin pathways is thought to predispose to vitiligo and melanocyte cytotoxicity. The teridines (6R)-L-erythro 5, 6, 7, and 8 tetrahydrobiopterin (6BH4) and (7R)-L-erythro 5, 6, 7, and 8 tertahydropterin (7BH4) are found in increased concentrations in vitiligo (24).

Theorizing accelerated cell senescence and apoptosis 7.

Among the abnormalities seen in melanocytes from non-lesional skin of vitiligo patients include nuclear DNA marginalization, cytoplasm vacuolization, rough endoplasmic reticulum dilatation, dendritic loss, and detachment. Apoptosis is seen in connection to keratinocytes in damaged vitiligo skin. As a consequence of cytoplasm condensation, vacuole development, and growth of membrane-bound organelles, basal and suprabasal epidermal cells in both normally pigmented and depigmented skin show signs of degeneration. (15)

8. Theory of viruses

Autoimmune hepatitis and chronic hepatitis C virus infection are the two main causes of vitiligo. Vitiligo patients tested negative for hepatitis B virus seropositivity, according to the research. Vitiligo may be worsened or etiopathogenesis may be aided by prior or continuing CMV infections. In addition, the link between vitiligo and other viruses, including herpes, hepatitis E, herpes simplex, and Epstein-Barr virus, is dubious. sixteen (16)

Therapy for vitiligo

Patients who are younger, have newly formed illness, have darker skin, and have lesions on their face, neck, or trunk are more likely to demonstrate a response to treatment. Despite not being treated well, the segmental form of vitiligo does not develop. The development and treatment resistance of vitiligo are associated with mucosal involvement, often acral lesions, and a familial history of the condition. Patients often endure psychological stress as a result of lengthy treatment durations and emotions of disappointment caused by prior treatment failures; psychotherapy serves an important purpose in alleviating this kind of stress. seventeen) Topical treatments

a) Steroids used topically

Since topical corticosteroids (TCS) work only in small, localized areas, they are still the therapy of choice for vitiligo. Preventing the production of autoantibodies against melanocytes is how corticosteroids function. Also proposed are five-day-a-week intermittent therapy regimens comprising three weeks of active treatment followed by one week of rest. It is recommended to discontinue therapy after three months if no noticeable improvement is shown. (number one)

inhibitors of calcineurin (b)

By blocking the nuclear factor of activated T cells' (NFAT) ability to induce proinflammatory cytokines, calcineurin inhibitors decrease T-cell activation. Although cyclosporine A has the best track record, it is not recommended for topical use because of its poor skin penetration. Tacrolimus and pimecrolimus are able to be administered topically to treat atopic dermatitis and other skin disorders due to their smaller molecular sizes. The main advantage is that they won't make your skin atrophy even after using them regularly for a long time. Because of this, they are great alternatives to topical corticosteroids

in areas that need them, such as the face and flexures. (c) a substitute for vitamin D (19)
In vitiligo, melanocytes supposedly disappear, but vitamin D protects the epidermal melanin unit and restores melanocyte integrity through a number of mechanisms, one of which is regulating melanocyte activation, proliferation, migration, and pigmentation pathways by modulating T cell activation. (20)
The d-group of antioxidants
The observation of a decrease in catalase enzyme in the epidermis of vitiligo patients and elevated levels of reactive oxygen species in lesional skin led to the theory that antioxidant treatment or other methods of reducing reactive oxygen species might be an effective treatment strategy. A variety of metal ions make up a therapeutic cream called pseudocatalase, which can convert the reactive oxygen species H2O2 into oxygen and water. (15) Extended medical care
(1) Corticosteroids administered systemically
Oral use of systemic corticosteroids in either low-dose or high-dose pulsed treatment has the potential to repigment vitiligo rapidly. (21)
2. Matsumotov
As a folic acid antagonist and cell proliferation inhibitor, methotrexate (MTX) considerably reduces the proliferation of T lymphocytes. By repressing B cell activity, it also blocks T cell activation and the production of intracellular adhesion molecules.Because it blocks the activity of T cells that may produce TNF alfa, 4 MTX has found value in the treatment of vitiligo. Hence, it has the potential to slow the advancement of illness.(22)
three. Inhibitors of JAK
The U.S. authorized ruxolitinib (Opzelura®, OPZ), a JAK inhibitor (JAKinh) that targets the IFN-γ and IL-15 signaling pathways, for the topical treatment of vitiligo because Janus kinase (JAK) is an intracellular tyrosine kinase that transmits signals from cytokines and growth factors. Japanese authorities have authorized ruxolitinib for AD since 2020, making it the second JAKinh for topical use in Japan after delgocitinib (Corectim®). Another oral JAKinh, ritlecitinib (Litfulo®), is now being tested in a clinical study for active vitiligo (23).

Targeted immunotherapy

Because it has been shown to be an essential signaling pathway for the development and maintenance of vitiligo, targeting the IFN-.. / CXCL10 axis might be a beneficial therapeutic strategy. A variety of antibodies and small molecule inhibitors that target various parts of this pathway (such as IFN-, CXCL10, and the CXCL10 receptor) have been shown to be safe in early-phase clinical trials for the treatment of other autoimmune disorders, including psoriasis, rheumatoid arthritis, and Crohn's disease. (204) Hormone that stimulates the production of melanocytes.
Because of its ability to lessen photosensitivity in erythropoietic protoporphyria, amelanotine has received approval from the European Medicines Agency. Therefore, amelanotine may also make phototherapy for vitiligo more successful. The darkening of healthy skin that amelanoside causes might highlight the pigmentation disparities between affected and healthy skin. Because this treatment option may create greater issues for lighter skin types, it has to be thought about while considering it. (25) Light treatments
Chapter One: Photochemotherapies
Psoralens and long-wave UVA radiation (320-340 nm) form the basis of PUVA, a photochemotherapy modality. Oral or topical administration of psoralens in the form of solutions, creams, or baths is possible, with subsequent exposure to UVA light. By photoconjugating psoralens to DNA, PUVA stimulates melanosome production and melanization, melanocyte proliferation, increased tyrosinase synthesis, and improved melanosome transfer to keratinocytes, hence promoting melanogenesis. The current phototherapy choice for active or extensive vitiligo is narrowband-ultraviolet B radiation (NB-UVB, 311 nm). It works just as well, if not better, than PUVA treatment, and it has less adverse effects. (27) Lightwaves
Researchers think it works by lowering whole body irradiation and negative effects on healthy skin by focused treatment with lasers, which is different from traditional light therapy. The monochromatic excimer laser (308 nm) outperforms conventional light therapy because it allows for targeted treatment of individual lesions. Itchy skin and mild reddening are typical complaints. (28)
3. A CO2 fractional laser
Evidence suggests that fractional laser treatment may enhance the topical distribution of a number of drugs, including as immunization, imiquimod, ascorbic acid derivatives, diclofenac, 5-fluorouracil (5-FU), and diclofenac. The vertical ablated laser channels are created when water absorbs a large amount of far-infrared light from a fractional laser operating at 2.940 to 10.600 nm. These channels enhance medication absorption via the skin by acting as microchannels. Photodynamic treatment has made use of fractional lasers to enhance photosensitizer absorption. (29) One theory regarding how ablative fractional CO2 lasers work to repigment vitiligo patients is that they

shrink the treated skin surface, which narrows the vitiliginous area. Another theory is that the lasers create microthermal channels, which improve medication absorption under the skin. A third theory is that, during the inflammatory phase, matrix metalloproteinase-2 is released, which may induce melanocytic stem cells to migrate from hair follicles to the vitiliginous areas. (30)

The drug 5-fluorouracil

Over time, 5-FU has shown promise in treating a number of dermatological conditions, thanks to its selective cytotoxicity and lack of influence on healthy skin cells. (31 1)

It is possible that 5-FU's immunomodulator qualities explain its efficacy in treating vitiligo when administered topically. Possible side effects include immunological suppression and stimulation of the depigmented epidermis's reserve of follicular or persistent Dopa-negative melanocytes. The repigmentation response may be enhanced by combining this topical treatment with spot dermabrasion of the vitiligo lesions. After six months of therapy, a 73.3% response rate was seen using a mix of spot dermabrasion and topical 5-fluorouracil. The use of topical 5-fluorouracil (5-FU) in conjunction with narrowband UVB (NB-UVB) therapy and pre-procedure treatments like laser ablation to increase skin penetration has been investigated as a potential treatment for vitiligo. (32) On acral areas, a combination of abrasive CO2 laser and 5-FU cream resulted in repigmentation of more than 50% in 55.9% of patients. In addition, they said that the treatment areas were infected, itchy, hyperpigmented, and painful. However, by using a fractional CO2 (FrCO2) laser in conjunction with a 5-FU solution, the present research was able to obtain comparable outcomes across several body regions while significantly reducing side effects and increasing safety. (33)

5. Restrictions and Ways Forward:

There is currently no cure for vitiligo, and no therapy has been able to reliably restore pigmentation in every patient. To discover novel therapeutic targets and get a better understanding of the pathophysiology of vitiligo, further scientific and clinical research is necessary. A plethora of novel treatments are in the works, with the majority of published details coming from case reports or series. But to find out how well they work, further randomized controlled studies are needed.

6. **Conclusions**:

The recurring nature of vitiligo and the lack of consistency in its clinical progress make therapy a source of frustration at times. Treatment plans should be tailored to each patient's unique vitiligo condition, level of activity, and drug's potential adverse effects.

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