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Vitiligo and Different Treatment Modalities

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Abstract
Objectives: Clinical trials comparing various vitiligo treatments for their effectiveness and safety. Setting the Scene: The characteristic white macules and patches seen in vitiligo, a prevalent depigmentation condition with an unexplained cause, are the outcome of the selective loss of melanocytes. Subtype, disease activity, vitiligo degree, treatment objectives, and other variables make vitiligo therapy difficult. Data Origins: For this purpose, we searched and analysed the Medline databases [Pub Med and Medscape] for papers that evaluated vitiligo treatment methods up to 2024. Research Question Selection: The inclusion of all research was determined by separate evaluations. Inclusion was contingent upon them meeting the following requirements: 1. The text was written and published in English. Published in journals that undergo a rigorous peer review process.3. Discuss the various methods used to cure vitiligo. When extracting data, studies were discarded if they did not meet the inclusion criteria. Considerations for judging the study's quality included whether or not it had received ethical clearance, the clarity of its eligibility requirements, the effectiveness of its controls, the quantity and quality of its data, and the clarity of its assessment tools. We used a data collecting form to independently extract information relevant to our research results from all qualifying studies. Conclusions: Vitiligo can be effectively treated using a variety of methods. The therapy of vitiligo is effectively and safely accomplished by combining microneedling with several topically administered drugs, such as botolnium toxin, topical trichloroacetic acid, and 5-fluorouracil.

Key words : Vinculosis, microneedling, 5-fluorouracil, trichloroacetic acid, botulinum toxin

Introduction

The gradual death of the skin's melanocytes is the cause of vitiligo, a chronic skin depigmenting illness that affects 0.5% to 1% of the population. [1]. Surgical procedures, antioxidants, systemic steroids, monochromatic excimer lasers, narrow-band ultraviolet B [NB-UVB], and topical treatments are among the many available therapeutic options. However, a full recovery from vitiligo is not guaranteed by any therapy. [2] Re-pigmentation in vitiligo may be possible with a shorter treatment time, fewer side effects, and an improved response when many modalities are used together [3].

It seems that microneedling vitiligo lesions causes melanocytes to migrate from the lesion's perimeter to its centre, which helps colour the lesion. [4]

In both hairy and non-hairy regions, melanocytes migrate from the perilesional skin to the centre of the afflicted areas during the re-epithelialization process, which is stimulated by TCA chemical stress [5].

5-fluorouracil [5-FU] stimulates the migration and proliferation of melanocytes, which in turn leads the vitiligo lesion to repigment [6]. This process is accomplished by the production of inflammatory mediators and metalloproteinases.

One subfamily of neurotoxins known as botulinum toxin [BoNT] may cleave target proteins of the SNARE complex, therefore blocking the release of acetylcholine and several other neurotransmitters from presynaptic vesicles. In terms of the cholinergic components of vitiligo pathogenesis, it was discovered that repigmentation restores normal expression of acetylcholinesterase and an increase in acetylcholine concentration in vitiliginous patches [7].

The tools and techniques

Data Origins: We searched the Medline databases [Pub Med and Medscape] for material on the decrease of vitiligo treatment methods up to 2022.

Research Question Selection: A thorough, impartial, and open selection procedure was used to identify the studies. Inclusion was contingent upon them meeting the following requirements:

First published in an English-language work. 2. Having one's work published in journals that use a rigorous system of peer review.3. Discuss the various methods used to cure vitiligo.

Research papers that failed to fulfil the inclusion criteria were not included in the data extraction process. The quality of the research was determined by many elements, including the presence or absence of ethical authorisation, eligibility criteria, controls, information, and well specified assessment methods. Using a data collection form, we independently extracted data pertinent to our

research findings from all qualifying studies that met our criteria.

Review of literature:

Varicose veins

White macules and patches appear all over the body in vitiligo, the most prevalent pigmentary skin ailment in the world [8]. This condition is caused by the death of pigmentary cells in the skin and hair. Vitiligo affects 0.5–1% of the population, and its incidence is not strongly associated with gender or race [9]. The unpredictable nature of vitiligo makes it difficult to anticipate when symptoms may flare up and when they will subside. It is possible for distinct vitiligo lesions in the same patient to relapse, remain stable, or advance at the same rate [10].

The causes and mechanisms of vitiligo

There are a lot of hypotheses on what causes vitiligo and the death of melanocytes. Theories such as oxidative stress, adhesion defect, autoimmune, neuronal, hereditary, and inflammatory mediator production are among these [11].

The genetic theory behind vitiligo suggests that it is a polygenic disorder, and several genes have been identified as potential causes, such as MHC, CAT, ACE, ILC, PTP, HLA, and CTLA-4 [12].

Model of Autoimmunity

When it comes to the pathophysiology of vitiligo, the autoimmune theory seems to be the most prominent and widely recognised. Cellular immunity, humoral antibody-mediated immunity, and cytokine activity may all mediate the immune response [13].

How the brain works:

According to the neurological explanation of vitiligo, abnormal responses of melanocytes to neuropeptides and catecholamines lead to their demise. The neuronal hypothesis has several arguments that are backed by clinical and laboratory evidence. The presence of thicker Schwann cell basement membranes and degraded and regenerated autonomous nerve fibres inside vitiligo lesions provides further evidence in favour of this theory [14].

Vitiligo patients experience oxidative stress due to a breakdown of anti-oxidative systems in their skin and blood. This lends credence to the idea that oxidative stress plays a part in the demise of melanocytes and the vitiligo lesion growth process. According to research, in-vitro vitiligo melanocytes are more susceptible to oxidative stress, which may cause cell death [15].

Fundamental principles:

Melanocytes in vitiligo, according to this view, die because of an innate flaw. Lesional skin melanocytes express less c-kit receptors, and there may be an irregular rough endoplasmic reticulum or an absence of basic fibroblast growth factor [bFGF] and other unknown melanocyte growth factors as part of this underlying abnormality [16].

Theorising adhesion defects:

According to this notion, vitiligo might be caused by poor cell adhesion. This is backed up by the fact that keratinocytes produce less extracellular matrix components, there are localised holes in the basement membrane, and the development of the membrane is impeded. As a result of these anomalies, melanocytes' basal attachment is impaired [17].

Vitiligo treatment

The goals of treating vitiligo are to halt the disease's progression, bring about repigmentation, and forestall recurrence. In most situations, the therapy is time-consuming, and in others, the results are less than ideal [18]. Although there are a number of current treatments for vitiligo, both surgical and non-surgical, none of them can ensure that the condition will go away entirely and permanently [19].

Application of corticosteroids topically

The face and neck, which are regions exposed to the sun, respond well to topical corticosteroids, which cause repigmentation in 75% of cases. We recommend using TCS everyday for at least three months. Following that, you may continue using an intermittent regimen for up to six months; however, after three to four months, you should stop using it [20].

Intradermal calcineurin inhibitors

Tacrolimus and tacrolimus are topical calcineurin inhibitors that influence T cell activation and maturation, which in turn inhibits the generation of cytokines including tumour necrosis factor [TNF] -α.16 There has also been mention of improving melanocyte migration and differentiation. In regions where the use of strong TCS for an extended period of time is not recommended, TCI has been shown to have positive benefits [21].

Alternatives to vitamin D3

Vitamin D3 analogues applied topically [D3A] have immunomodulatory actions that decrease T-cell activity, improve melanocyte formation, and induce melanogenesis; nonetheless, they are not effective monotherapy for vitiligo and are better used as adjuvants to other treatments. Applying a mixture of calcipotriol 0.005% and betamethasone 0.05% topically over 30% of the body for 4 weeks with the ointment and 8 weeks with the cream is the maximum dosage suggested [22].

Spectral UVB

In vitiligo, nb-UVB phototherapy [with a wavelength of 311 nm] works by suppressing the immune system, which in turn triggers the differentiation of melanocytes, increases melanin synthesis, and causes melanocyte migration from the periphery of the skin. The Vitiligo Working Group suggests three weekly sessions of nb-UVB phototherapy as the best frequency of delivery [23].

Combination ultraviolet A [UVA] and psoralen photochemotherapy

Photoconjugation of psoralens to DNA promotes melanocyte proliferation, enhanced tyrosinase production, creation and melanization of melanosomes, and increased transfer of melanosomes to keratinocytes, all of which are involved in PUVA-induced acceleration of melanogenesis [24].

Treatment with a laser Energetic light

The process works by stimulating the migration and proliferation of melanocytes in hair follicles and having a direct cytotoxic impact on T lymphocytes. The 308-nm excimer laser therapy was shown to be more effective than NB-UVB in causing repigmentation, according to a research [25].

Medical microneedling

During the healing phase, keratinocytes and melanocytes migrate due to trauma-induced inflammation. Cytokines and growth factors, such as TGF-α, TGF-β, and PDGF, influx into the area, stimulating melanocytes on the edge of the patch or outside the wound. These are the hypothesised mechanisms that cause repigmentation following needling. pigmented hair's root sheath and the mechanical movement of melanocytes from the border regions to the unpigmented regions. When stable vitiligo treatments are ineffective or take too long to take effect, a straightforward and harmless technique called needling may help stimulate more pigmentation [26].

To deliver their active ingredients deep into the skin, microneedles puncture it via a network of microscopic holes in the dermis. As the microneedle rolls over the skin, it may stimulate the dermis to produce more collagen and fibroblasts. In order to transplant vitiligo melanocytes, microneedles were inserted into the skin in the leucoplakia region. Administering a drug through microneedles into the skin can induce hyperplasia of epidermal stem cells in situ, which then differentiate into melanocytes and repair damaged melanocytes. This improves microcirculation to the injured area, fixes leucoplakia, and may be useful in treating vitiligo [27].

Because microneedling produces stratus corneum micropores, it may speed up transdermal drug delivery.It is crucial to choose the right kind of microneedle; for example, lengthy needles might possibly cause bleeding, which can prevent the absorption of certain drugs. But microneedling may make photodynamic therapy more effective and speed up the pace at which topical treatments are delivered to the dermis [28].

An accessible, office-based, cost-effective, and relatively risk-free option for treating vitiligo is trichloroacetic acid [TCA]. [29] Using TCA alone or in conjunction with microneedling both provide positive outcomes [30].

Trauma caused by TCA application on vitiligo areas can lead to perifollicular pigmentation in hairy areas. This is because trauma is believed to induce hyperpigmentation in two ways: first, by destroying the basal cell layer and accumulating melanophages in the upper dermis; second, by inducing a tyrosine kinase response that extends from the epidermis to the late dermis, where growth factors, proteases, and extracellular matrix components are upregulated. Repigmentation occurs when melanin production increases and is transferred to neighbouring keratinocytes as a result of this inflammatory response [30].

Metformin [5-FU]

One chemotherapy drug that often induces hyperpigmentation at injection sites is 5-fluorouracil [5-FU]. When used alone or in conjunction with other therapies, like as microneedling, it has been shown to be effective in treating vitiligo. number three.

There are a number of hypotheses that attempt to describe how 5-fluorouracil works in conjunction with needling. An inflammatory response occurs in response to a wound, and the production of leukotrienes and other inflammatory mediators stimulates the melanocytes. Local oedema also expands the gaps between cells in the dermal basement membrane. Therefore, active melanocytes move towards the achromic regions during re-epithelialization. When 5-FU was administered in conjunction with dermabrasion, a pseudomembrane with surrounding erythema was sometimes seen, however this was not the case when dermabrasion was administered alone. One new approach to treating stable vitiligo is microneedling followed by 5-fluorouracil used topically [32].

The neurotoxin botulinum [Botox]

Acetylcholine, acetylcholine receptors, and ACh metabolism-related enzymes have been implicated in melanogenesis in many investigations. [number 33]. Sunlight, for instance, stimulates keratinocytes in the epidermis to secrete ACh; an AChE inhibitor reduced this effect of light on melanogenesis.

Thus, it is plausible that Ach inhibits melanogenesis and that AChE promotes melanogenesis [34].Additionally, it was shown that vitiliginous patches, which repigment to normal after a large decrease in acetylcholinesterase production, had an enhanced acetylcholine content [35].

References

[1] K, Ezzedine J, Seneschal A, Da Silva N, Préaubert A, Lamblin C, Delattre C, Emery C, Nevoret J, Finzi S, Bouée T Passeron. Vitiligo patient population and disease burden in France: VIOLIN study results from the CONSTANCES cohort. Journal of the European Academy of Dermatology and Venereology. Nov;vol,37[11]:pp:2249-58. 2023.

[2] Y. M. E., Neinaa, S. S., Lotfy, N. R. Ghaly, & N. N. Doghaim, A comparative study of combined microneedling and narrowband ultraviolet B phototherapy versus their combination with topical latanoprost in the treatment of vitiligo. Dermatol Ther, vol, 34,pp: e14813. 2021.

[3] M.I. AlJasser, and S, Altalhab. S. Controlled depth of needling using simple injection needles. J Am Acad Dermatol.;vol, 20:pp:0190–9622. 2020.

[4] M, Roohaninasab P, Mansouri F, Seirafianpour AJ, Naeini A Goodarzi. Therapeutic options and hot topics in vitiligo with special focus on pediatrics' vitiligo: a comprehensive review study. Dermatol Ther. 2021; vol, 34[1]:pp: e14550.

[5] A, Nofal F, Eldeeb M, Shalaby W Al-Balat. Microneedling combined with pimecrolimus, 5-fluorouracil, and trichloroacetic acid in the treatment of vitiligo: A comparative study. Dermatologic therapy. 2022 Mar;vol, 35[3]:pp:e15294.

[6] FT, Zahra M, Adil SS, Amin M, Mohtashim R, Bansal HQ Khan. Efficacy of Topical 5% 5-Fluorouracil with Needling versus 5% 5-Fluorouracil Alone in Stable Vitiligo: A Randomized Controlled Study. J Cutan Aesthet Surg. 2020 Jul-Sep;vol,13[3]:pp:197-203.

[7] AM,Chivu E, Balasescu RI, Nedelcu A, Brinzea M,Antohe A, Coman G, Turcu I, Hulea DA Ion. Vitiligo–from clinical manifestations to pathophysiological mechanisms and cell death. Romanian medical JouRnal. 2021;ovl, 68[2]:pp:148.

[8] ME Mazzei Weiss. Vitiligo: to biopsy or not to biopsy? Cutis. 2020;vol,105 [4]:pp:189-190.

[9] R, Jakku V, Thappatla T, Kola RK Kadarla. Vitiligo – an overview. Asian J Pharm Res Dev 2019; vol,7:pp:113–23.

[10] D, Rosmarin AM, Soliman S, Marwaha J, Piercy HS, Camp P, Anderson K Ezzedine. Disease Course, Treatment Patterns and Goals Among Patients with Non-segmental Vitiligo Across Europe and the United States. Dermatology and Therapy. 2024 Jun vol,26:pp:1-3.

[11] F, Shah S, Patel R, Begum M Dwivedi. Emerging role of Tissue Resident Memory T cells in vitiligo: From pathogenesis to therapeutics. Autoimmun Rev. 2021 Aug;vol, 20[8]:pp:102868.

[12] M, Imran VR, Leite-Silva M Yousuf. Vitiligo: A Review of Aetiology, Pathogenesis, Treatment, and Psychosocial Impact. Cosmetics. 2023;vol, 10[3]:pp:84.

[13] ML, Frisoli K, Essien JE Harris. Vitiligo: Mechanisms of Pathogenesis and Treatment. Annu Rev Immunol. 2020 Apr 26; vol,38:pp:621-648

[14] A, Kussainova L, Kassym A, Akhmetova N, Glushkova U, Sabirov S, Adilgozhina R, Tuleutayeva Y Semenova. Vitiligo and anxiety: A systematic review and meta-analysis. PLoS One. 2020 Nov vol,10;15[11]:pp:e0241445.

[15] K,AL-smadi M,Imran VR, Leite-Silva Y Mohammed. Vitiligo: A Review of Aetiology, Pathogenesis, Treatment, and Psychosocial Impact. Cosmetics.; vol,10[3]:pp:84.2023

[16] RL, Belote D, Le A, Maynard UE, Lang A, Sinclair BK, Lohman V, Planells-Palop L, Baskin AD, Tward S, Darmanis RL Judson-Torres. Human melanocyte development and melanoma dedifferentiation at single-cell resolution. Nature Cell Biology. 2021 Sep;vol,23[9]:pp:1035-47.

[17] D.; Kovacs, E.; Bastonini, S.; Briganti, M.; Ottaviani, A.; D'Arino, M.; Truglio, L.; Sciuto, M.; Zaccarini, A.; Pacifico, C.; Cota, et al. Altered epidermal proliferation, differentiation, and lipid composition: Novel key elements in the vitiligo puzzle. Sci. Adv. 2022, vol, 8, eabn9299

[18] RA, Vreman I, Heikkinen A, Schuurman C, Sapede JL, Garcia N, Hedberg D, Athanasiou J, Grueger HGM, Leufkens WG Goettsch. Unmet

Medical Need: An Introduction to Definitions and Stakeholder Perceptions. Value Health. 2019;vol,22[11]:pp:1275–1282.

[19] J Seneschal. Clinical features of vitiligo and social impact on quality of life. Dermatology Practical & Conceptual. 2023 Dec;vol,13[4 Suppl 2].

[20] V, Relhan A, Kaur A Bagrodia. Newer topical therapies in vitiligo: A comprehensive review. Indian Journal of Drugs in Dermatology. 2023 Jul vol,1;9[2]:pp:45-52.

[21] T, Lotti K, Agarwal I, Podder F, Satolli M, Kassir RA, Schwartz U, Wollina S, Grabbe AA, Navarini SM Mueller and M Goldust: Safety of the current drug treatments for vitiligo. Expert Opin Drug Saf. vol,19:pp:499–511. 2020

[22] K, Al-Smadi M, Ali SE, Alavi X, Jin M, Imran VR, Leite-Silva Y Mohammed. Using a Topical Formulation of Vitamin D for the Treatment of Vitiligo: A Systematic Review. Cells. Sep vol, 30;pp:12[19]:2387. 2023.

[23] YJ, Phulari R, Kukreja RN, Hiremath CC, Patil P Patel. Vitiligo: Prevalence, Clinical Patterns, and Efficacy of Narrow Band Ultraviolet B Phototherapy. Clinical Dermatology Review. 2023 Apr vol,1;7[2]:pp:153-7.

[24] V, Lajevardi ZS, Hosseini S Heidari. Efficacy of using oral methotrexate with phototherapy in the treatment of vitiligo in comparison with single phototherapy treatment: a double-blinded randomized controlled trial. Photodermatology, Photoimmunology & Photomedicine. 2023 Nov;vol,39[6]:pp:657-62.

[25] TT, Yang SH, Chiu CE Lan. The effects of UVB irradiance on vitiligo phototherapy and UVB-induced photocarcinogenesis. Photodermatol Photoimmunol Photomed. 2020 Jul;vol,36[4]:pp:257-262.

[26] A, Salloum N, Bazzi D, Maalouf M Habre. Microneedling in vitiligo: a systematic review. Dermatol Ther. 2020; vol,33[6]: pp:e14297.

[27] He, Tao Li Gong, "Clinical Effect of Microneedle Injection Combined with Blood Transfusion in the Treatment of Severe Anemia Complicated with Vitiligo under Regenerative Medical Technology", BioMed Research International, vol. 2022p 12.

[28] E, Lima M, Lima H Miot. Histopathological Evidences of the Percutaneous Collagen Induction with Microneedling. Percutaneous Collagen Induction With Microneedling: A Step-by-Step Clinical Guide. 2021:pp:59-67.

[29] M Mukhtar. Trichloroacetic acid cautery for repigmenting nonresponsive vitiligo on lips. Journal of Cutaneous and Aesthetic Surgery. 2023 Apr vol,1;16[2]:pp:154-5.

[30] M., Khater, M., Nasr, S. Salah, and F.M., Khattab. Clinical evaluation of the efficacy of trichloroacetic acid 70% after microneedling vs intradermal injection of 5-fluorouracil in the treatment of nonsegmental vitiligo; a prospective comparative study. Dermatologic Therapy, vol,33[4], pp: e13532. 2020.

[31] FT, Zahra M, Adil SS, Amin M, Mohtashim R, Bansal HQ Khan. Efficacy of topical 5% 5-fluorouracil with needling versus 5% 5-fluorouracil alone in stable vitiligo: a randomized controlled study. J Cutan Aesthet Surg. 2020; vol,13[3]: pp:197-203.

[32] S,Chhabra YS, Chahar A Singh. A Comparative Study of Microneedling Combined with Topical 5-Fluorouracil versus Microneedling Alone in Treatment of Localized Stable Vitiligo. Indian J Dermatol. 2021 Sep-Oct.vol,;66[5]:pp:574

[33] E, Enkhtaivan CH Lee. Role of Amine Neurotransmitters and Their Receptors in Skin Pigmentation: Therapeutic Implication. Int J Mol Sci. 2021 Jul vol,28;pp:22[15]:8071

[34] Q., Wu Y., Xia K., Dai P.,Bai K.K.L., Kwan M.S.S., Guo T.T.X., Dong K.W.K. Tsim Solar light induces the release of acetylcholine from skin keratinocytes affecting melanogenesis. FASEB J. 2020; vol,34:pp:8941–8958.

[35] LA, Hokky MR,Saraswati NP, Sriwidyani IG, Artini IP, Widyadharma KK Winaya. Effect of botulinum toxin A on tyrosinase and melanin: A literature review. Indonesia Journal of Biomedical Science. 2024 May vol,28;pp: 18[1]:110-5