ŚLUSARCZYK, Daniel, ŻMUDA, Bartłomiej, JAKUBOWSKA, Wiktoria, PISERA, Piotr, KIEŁKOWICZ, Aleksandra, POPIŃSKA, Zuzanna, PACTWA, Filip and ŻUBEREK, Michal. Reviewing the current treatment approaches for vitiligo – analysis of literature. Journal of Education, Health and Sport. 2023;49(1):11-26. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2023.49.01.001
https://apcz.umk.pl/JEHS/article/view/47540
https://zenodo.org/records/10435298

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 03.11.2023 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Health Sciences (Field of medical and health sciences); Medical sciences (Field of medical and health sciences); Cultural and religious studies (Field of humanities); Physical culture sciences (Field of medical and health sciences); Socio-economic geography and spatial management (Field of social sciences); Pedagogy (Field of social sciences); Earth and Environmental Sciences (Field of exact and natural sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 03.11.2023 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki medyczne (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o kulturze i religii (Dziedzina nauk humanistycznych); Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Geografia społeczno-ekonomiczna i gospodarka przestrzenna (Dziedzina nauk społecznych); Pedagogika (Dziedzina nauk społecznych); Nauki o Ziemi i środowisku (Dziedzina nauk ścisłych i przyrodniczych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.12.2023. Revised: 26.12.2023. Accepted: 27.12.2023. Published: 30.12.2023.

Reviewing the current treatment approaches for vitiligo – analysis of literature

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Abstract

Introduction:

Vitiligo is a relatively common systemic, idiopathic disease within the spectrum of pigmentary disorders. Clinically, it presents as depigmented patches on the skin, resulting from the loss or dysfunction of melanocytes. Despite not impacting life expectancy, vitiligo should not be perceived merely as a cosmetic defect, given its potential to burden daily life and the frequent experiences of stigmatization by patients.

Aim of the study:

The aim of this study was to summarize the existing knowledge regarding the treatment of vitiligo. The current treatments in practice, alongside potential new methods, were summarized and described.

Materials and methods:

The literature available in the PubMed database was reviewed using the following keywords: "Vitiligo", "Vitiligo treatment", "Vitiligo new treatment methods", "Targeted therapies for vitiligo".

Conclusions:

Vitiligo is a multifactorial and still inadequately understood disorder, leading to a lack of fully safe and effective treatment. As in the management of other diseases, there should be a push for highly personalized treatments for patients. This approach takes into account the differences among patients and ensures a better chance of a positive clinical response. To achieve this goal, it's necessary to explore new treatment methods and expand ongoing research efforts. Also, raising awareness of vitiligo is key to increasing acceptance, support and understanding for those affected by the disease.

Key words: Vitiligo; Therapeutics; Molecular Targeted Therapy

Introduction

The first references to vitiligo can be found in Egyptian and Indian texts and are dated to around 1500 BC. The stigma with which people suffering from vitiligo were burdened has been discernible since those days [1]. Early Buddhist texts indicate that people with vitiligo were excluded from being ordained as priests, while Hindu texts suggest that those with the disease may have been prone to stealing clothes in a previous life [2]. Vitiligo is a common skin pigmentation disorder, with an estimated prevalence of 0.5-2% of the population worldwide. It is usually characterized by multiple, discoloured patches of various shapes and sizes, without inflammation or atrophy, with a distinct border. They occur with equal frequency in children and adults [3]. Individuals diagnosed with vitiligo, particularly those with darker skin tones, may face stigma, leading to adverse effects on their mental well-being and overall quality of life [4]. Due to the prevalence of this disease and its multifaceted consequences, it requires improving treatment methods and tailoring them to the individual patient.

Etiology

Vitiligo is a disease characterized by the development of well-circumscribed discoloured patches caused by loss or dysregulation of melanocyte function [5]. However, the etiology of vitiligo has not been clearly explained. Many hypotheses have been developed regarding the role of innervation, vascular abnormalities, oxidative stress, melanocyte adhesion defect, autoimmunity, and genetic background [6]. We will focus on selected hypotheses that have relevant evidence to support them.

Neural Theory. According to this theory, innervation affects skin depigmentation. For some patients, lesions present unilaterally or involving one dermatome have been observed, but rarely the disease is limited to one dermatome [7]. Some researchers have hypothesized that vitiligo is associated with changes in the concentrations of neuropeptides and biogenic amines (e.g. catecholamines), which is thought to translate into decreased melanin production in melanocytes [8, 9]. There are reports of cases of vitiligo acquired as a result of limb denervation due to trauma. However, cases of quite the opposite - repigmentation after denervation - are also described [10]. Changes in sweat secretion by areas of skin affected by vitiligo have also been reported [11]. Since these studies are largely inconclusive no premature conclusions should be drawn. The appearance of the first symptoms or exacerbation of existing ones under stress is also a well-known fact, but this is an observation common to many autoimmune diseases.

Autoimmunity Theory. According to this theory, self-reactive immune cells attack melanocytes, leading to their death and loss from the skin. This theory seems very plausible considering the fact that people with vitiligo may co-occur with another autoimmune disease, such as Hashimoto's disease, type I diabetes, Addison’s disease [12]. Studies have shown the presence of autoantibodies against melanocytes only in vitiligo patients and not in healthy controls. Subsequent studies brought new observations. It turned out that antibodies can be formed in vivo by skin grafts, their presence does not correlate with the severity of the disease, and they are evenly distributed throughout the skin. They also report infiltration of the skin by CD8+ T cells and the release of damage-associated molecular patterns (DAMPs) [13, 14]. Although autoantibodies indicated an immune response against melanocytes it became clear that melanocyte damage was due to another mechanism.

Microvascular Theory. This theory is based on the observed increased blood flow within the vitiligo skin. The increased blood flow may enhance the migration of melanocyte-specific T

lymphocytes from regional lymph nodes and lead to their destruction. However, there's an intriguing paradox: when vitiligo arises in melanoma patients due to a vaccine that stimulates the growth of melanocyte-specific T cells, the condition tends to manifest in a nonsegmental manner, contrary to expectations. If the microvascular theory held true, one would anticipate its development to follow a segmental pattern, starting from the site of injection [15, 16].

Melanocyte Adhesion Theory. It suggests that melanocytes lose or have reduced adhesion to the skin, and can therefore be easily eliminated during oxidative stress or mechanical pressure. Some studies report reduced expression of E-cadherin on melanocytes, while others found no significant differences compared to the skin of a healthy person. Reduced adhesion may also be a response to the release of large amounts of autoantigens or internal defects in coping with oxidative stress [17, 18].

Degenerative Theory. It focuses on the premise that there is an intrinsic defect in melanocytes that leads to their loss in the skin. It stems from observations of impaired culture of melanocytes taken from people with vitiligo compared to melanocytes from healthy individuals. It has also been reported that there is a disruption of reactive oxidation species (ROS) and increased susceptibility to ROS-inducing substances [19].

Genetics. Genetics clearly influence the risk of developing acquired vitiligo, although it should not be described as a theory in itself. This is evidenced, for example, by the significantly higher incidence of the disease if there are relatives with vitiligo. Genetic studies to date have focused on patients with non-segmental vitiligo. Whole-genome association studies are the "gold standard" for detecting genes responsible for predisposition to the development of vitiligo. About 90% of "suspect" genes encode immunoregulatory proteins, while the remaining 10% encode melanocyte proteins [20].

As can be seen, despite the numerous hypotheses, none of them individually explains the etiology of the disease in no uncertain terms.

Diagnosis

The diagnosis of vitiligo is based primarily on the results of the physical examination and patient history, and in uncertain cases also on the results of additional tests. The patient's age, gender, genetic history, history of autoimmune diseases, ethnicity, psychological analysis, disease onset, course and stability should be taken into account in the history. Exposure to

factors that may trigger or exacerbate vitiligo, such as stress, infections, trauma, systemic medications taken, the presence of other comorbidities and their therapy, should also be investigated. It is also important to consider previous attempts at repigmentation (type and length of therapy used) and their effects. During the physical examination, the doctor evaluates the location, colour, size, shape and borders of the patches of acquired vitiligo. In addition, he identifies the type of repigmentation (mixed, centered on the hair follicles or margins, or peripheral), checks for the presence of Sutton's nevi, analyses the condition of the nail plate and hair, and evaluates the colour of the iris and its uniformity in both eyes [21]. For fair-skinned individuals, a Wood's lamp can be helpful to determine the extent of skin lesions and facilitate differential diagnosis. The examination is best performed in a dark room. The conclusive test in case of diagnostic difficulties is histopathological examination [22].

Classification

According to the Vitiligo Global Issues Consensus Conference guidelines, vitiligo is divided into segmental vitiligo (SV), non-segmental vitiligo (NSV) and unclassified vitiligo. Non-segmental vitiligo can be divided into: focal, mucosal, acrofacial, generalized and universal, while segmental vitiligo into several subtypes: focal, mucosal, unisegmental, bisegmental and multisegmental. This division is important because SV and NSV differ in their course, treatment options and prognosis [23].

Treatment

In order to make this summary of available treatments clear, it will be divided into the following sections: topical treatment, phototherapy and laser therapy, systemic treatment (including targeted treatment), surgical treatment and other methods.

Topical treatment

Topical treatment is usually applicable when the area of skin involved is <20%.

Topical corticosteroids. The mechanism of action of corticosteroids is based on local immunomodulation and stimulation of melanocytes. They reduce the expression of cytokines such as interleukins, interferon-γ and TNF-α. Thus, they inhibit the activation of cytotoxic T lymphocytes and reduce the response of B lymphocytes to their own host antigens. In non-

segmental vitiligo, about half of patients achieve repigmentation >75% using class III and IV corticosteroids. Steroids of lower classes have higher efficacy, but their use is fraught with more severe side effects such as skin atrophy, telangiectasia, striae, folliculitis or acne-like lesions. Betamethasone valerate (class III), for example, shows greater efficacy than mometasone furoinate (class IV), but its long-term use is associated with more side effects. Topical corticosteroids also have slightly higher efficacy than calcineurin inhibitors. Better results are obtained when they are used in combination. It should also be noted that the use of corticosteroids on a large area of skin may be associated with the penetration of significant amounts into the blood and also systemic effects. At this point, reference should be made to the treatment of children, in whom strong corticosteroids applied to a large surface area can lead to inhibition of the hypothalamic-pituitary-adrenal (HPA) axis [24, 25, 26, 27].

Topical calcineurin inhibitors. This group of drugs has a similar mechanism of action to steroids, including by blocking the synthesis of interleukins (such as IL-2) and TNF-α. The flagship drug of this group is tacrolimus. Studies have shown a better repigmentation effect for tacrolimus compared to placebo and compared to clobetasol (tacrolimus 0.1% ointment vs clobetasol 0.05% ointment). The effects of pimecrolimus treatment are worse than those of clobetasol. Both of these calcineurin inhibitors are particularly useful in the treatment of facial lesions. The efficacy of treating lesions on the face with them was higher than on the trunk and extremities. In addition, they are not fraught with many of the side effects mentioned in the previous section on topical corticosteroids (mainly such as skin atrophy and telangiectasias). They may have side effects like erythema, itching or burning [28, 29, 30].

Topical Vitamin D analogues, topical prostaglandin analogues, topical antioxidants. Alternative preparations possible in topical form. Only a fraction of patients benefit from their use. Attempts have been made to combine them with phototherapy with varying results [31].

Phototherapy and laser therapy

Phototherapy is considered a first-line treatment for vitiligo with >10% surface involvement.

PUVA-Psoralen plus UV-A and narrow band UV-B (NB-UVB). The methods differ in the wavelength of the light used: UV-A 320-380 nm, UV-B 311 nm. In addition, PUVA uses psoralen, which has the ability to increase skin sensitivity to ultraviolet light. For both methods, it is noticeable that a better clinical response is obtained with longer phototherapy time - significantly higher repigmentation percentages >75% for a 12-month period compared to 6-month periods. NB-UVB 311 nm is more effective and has a lower risk of side effects.

We speak of effective phototherapy if repigmentation was observed during the first 3 months of treatment (or the degree of repigmentation was less greater than or equal to 25% after 6 months of therapy. During periods during the year with high sun exposure, it can be replaced by heliotherapy. In addition, phototherapy can be combined with topical medications such as corticosteroids, calcineurin inhibitors or surgical treatment, which will be discussed later [25].

Lasers: monochromatic excimer laser (MEL) and helium neon laser. The analysis showed for MEL 308 nm laser therapy a repigmentation of >75% in about 25% of patients, while for the helium-neon laser, 60% of patients achieved a repigmentation of more than 50%. The best results were seen for lesions on the head and neck. Lasers may give better results than NB-UVB and work better in combination with topical therapy [32, 33].

Systemic treatment

The main drugs used for systemic treatment are oral corticosteroids and azathioprine, with the former being a second-line treatment in patients who do not respond well to topical treatment and phototherapy. Large clinical trials have shown disease stabilization in about 90% of patients taking dexamethasone 2.5 mg twice a week and some repigmentation. However, one in ten patients had a relapse. Also, approx. 10% of patients reported side effects - mainly weight gain and acne-like eruptions. Satisfactory repigmentation rates were shown for azathioprine, especially when it was combined with PUVA. The efficacy of azathioprine (50 mg daily for 6 months) was comparable to betamethasone administered in pulses [34, 35]. Of the other drugs that can be used for systemic treatment, minocycline was studied and showed similar efficacy with pulse corticosteroids in terms of inhibiting disease activity. Methotrexate also showed such efficacy. In its case, sun-exposed lesions responded best. Cyclosporine was also capable of inducing repigmentation. However, both methotrexate and cyclosporine use are associated with significant side effects [37, 38, 39]. Relatively new drugs that can be used in the systemic treatment of vitiligo are JAK-STAT inhibitors. Tofacitinib and ruxolitinib can be included in this group. Studies using tofacitinib have shown that with 5 mg twice a day, it is possible to achieve complete repigmentation of lesions on the face and hands in cases of progressive vitiligo after treatment lasting 5 months. Also, studies have shown a excellent response to combination treatment with tofacitinib along with exposure to NB-UVB or sunlight. Patients achieved 92% repigmentation. In most patients, tofacitinib was well tolerated, with upper respiratory tract infections and diarrhea being among the most common side effects. With ruxolitinib taken 20 mg twice daily for 20 weeks, treatment was not satisfactory. Facial lesions showed transient improvement and then recurred. However,

ruxolitinib applied topically, in the form of a 1.5% cream twice a day performed significantly better. An average improvement of 27% was noted. Similar to tofacitinib, combination treatment with NBUVB resulted in very good repigmentation [40]. Statins were also being evaluated as possible drugs for systemic treatment after a 55-year-old man treated for hypertension taking simvastatin was observed to regress his white spots. Results in laboratory animals were good, but in a double-blind, placebo-controlled phase II clinical trial, a worsening of the disease was observed in the group taking simvastatin. There was an average increase in the VASI score of 26% in this group [41]. Studies on afamelanotide [Nle4-D-Phe7]-α-MSH for the treatment of vitiligo have shown it to be an effective therapy, demonstrating greater efficacy than NB-UVB monotherapy. It affects melanogenesis by stimulating the melanocortin 1 receptor (MC1R) and rebalances the cytokine milieu by acting on inflammatory cells expressing MC1R. However, although the therapy was effective, some participants withdrew from the study due to socially unacceptable skin hyperpigmentation [42].

Surgical treatment

So far, a great number of surgical treatments for vitiligo have been developed, including split thickness skin grafts, mini punch grafts, blister roof grafts, cellular grafts and others. The standard technique is suction blister epidermal grafting. It is performed by transferring epidermal grafts from a donor site (usually the thighs or arms) to a recipient site, usually pre-treated with dermabrasion. The grafts, in turn, are obtained from the roof of subepidermal blisters, created by prolonged application of vacuum to the donor site. Surgical treatment can only be considered in patients with stable disease (no new vitiligo lesions and no progression of existing lesions for 6 months). Surgical treatment is preferred as the first line of therapy for lesions located on the dorsal parts of the hands and feet, and when other treatments have been unsuccessful [36].

Other methods of treatment

Other methods of treatment that do not fall into the categories listed above should also be mentioned in this paper. Such methods include various cosmetic treatments based on masking vitiligo lesions, especially in patients with reduced quality of life. They play a major role in patients with contraindications to the standard treatment used, who do not agree with the treatment or the treatment used has not had a satisfactory effect. In addition, camouflage can

be used during standard therapy as long as it does not hinder treatment (use with topical medications or phototherapy may not be possible) [43].

For those with a very large area of skin occupied by vitiligo, depigmentation therapy of the remaining healthy skin may be considered. Such treatment should be considered in patients with <20% healthy skin. Hydroquinone monobenzyl ether or ruby laser is used as a depigmenting agent [43].

Psychological and psychiatric support plays a key role as an adjunct to medical therapy for vitiligo. Patients often experience emotional challenges associated with the loss of skin pigmentation, which can lead to lowered self-esteem, depression and social anxiety. Psychological therapy helps manage these emotions, improving well-being and quality of life. By providing emotional support and coping with psychological difficulties, patients can better tolerate treatment and achieve better outcomes. Integrating medical care with psychological support is key to comprehensive care for vitiligo patients [44].

Conclusions

Vitiligo is a complex condition influenced by multiple factors, yet its exact causes remain unclear, leading to a lack of certain and effective treatment options. The prolonged nature of the condition and the challenge of lengthy treatment, which offers limited effectiveness, have taken a toll on patients' emotional well-being, contributing to a significant number of individuals experiencing psychological distress. As in the management of other diseases, there should be a push for highly personalized treatments for patients. This approach takes into account the differences among patients and ensures a better chance of a positive clinical response. There should be a move away from drugs that are difficult for patients to use and fraught with numerous side effects. Targeted drugs like JAK-STAT inhibitors are proving promising. Patients treated with them have achieved up to 92% repigmentation when combined with NB-UVB or heliotherapy. However, the cost of this type of treatment remains a problem at this point.

Author's contribution

Conceptualization, Daniel Ślusarczyk and Bartłomiej Żmuda; methodology, Daniel Ślusarczyk and Wiktoria Jakubowska; software, Filip Pactwa and Wiktoria Jakubowska;

check, Bartłomiej Żmuda and Aleksandra Kiełkowicz; formal analysis, Daniel Ślusarczyk and Piotr Pisera; investigation, Daniel Ślusarczyk and Aleksandra Kiełkowicz; resources, Filip Pactwa and Zuzanna Popińska; data curation, Piotr Pisera, Michał Żuberek; writing - rough preparation, Daniel Ślusarczyk; writing - review and editing, Daniel Ślusarczyk and Wiktoria Jakubowska; visualization, Daniel Ślusarczyk, Bartłomiej Żmuda and Michał Żuberek; supervision, Bartłomiej Żmuda and Piotr Pisera; project administration, Daniel Ślusarczyk, Zuzanna Popińska. All authors have read and agreed with the published version of the manuscript.

Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

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