doi: http://dx.doi.org/10.11606/issn.1679-9836.v99i3p278-285 Rev Med (São Paulo). 2020 May-June;99(3):278-85.

Aspectos sobre a etiopatogênese e terapêutica do vitiligo

Aspects of etiopathogenesis and therapy of vitiligo

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Mendonça AEA, Aquino DD, Horbilon JAM, Rocha Sobrinho HMR. Aspects of etiopathogenesis and therapy of vitiligo / *Aspectos sobre a etiopatogênese e terapêutica do* vitiligo. Rev Med (São Paulo). 2020 May-June;99(3):278-85.

ABSTRACT: Introduction: Vitiligo is a chronic skin disease characterized by cutaneous depigmentation, being associated with aesthetic disfiguration and considerable psychological discomfort, representing great challenges in terms of dermatological care. Main Objective: To address the etiopathogenic aspects of vitiligo, as well as to present current therapeutic options for disease management. Method: Narrative bibliographic review using the electronic Pubmed database (US National Library of Medicine). The research was carried out in 2018, using the following identifiers in Health Sciences: vitiligo, cosmetic camouflage and vitiligo, treatment and vitiligo, physiopathology and vitiligo, immunopathology and vitiligo. We selected 26 researches published in the period from 2011 to 2018 that presented contents related to the objectives of this study. Result: Vitiligo is developed by the association of a genetic predisposition and exposure to environmental factors. The treatment aims to limit the progression of the disease, promote repigmentation of the affected areas and prevent relapses; It can be divided into clinical, aesthetic and surgical. Topical, systemic, phototherapy and recent immunobiological medicines are clinical treatments. The aesthetic treatment is represented by cosmetic camouflage and the surgical one is indicated for those who present stable disease not responsive to clinical therapy. Conclusion: Treatment is usually performed by the association of techniques, which is why it should be individualized for each patient. Early initiation of treatment is associated with a more favorable prognosis of the disease. It is of extreme importance not to neglect it in addition to knowing therapeutic innovations, considering the potential societal stigmatization of the disease, as a result improving clinical practice and quality of life of patients.

.**Keywords:** Vitiligo, Autoimmunity, Repigmentation, Drug Therapy, Phototherapy, Cosmetic, Surgery, Tissue Graft.

RESUMO: O vitiligo é uma doença cutânea crônica caracterizada por despigmentação da pele, sendo associada com desfiguração estética e considerável desconforto psicológico, representando grandes desafios em termos de cuidados dermatológicos. A partir do conhecimento do impacto psicossocial desta doença para o paciente e os desafios do seu tratamento pela medicina, este trabalho teve como objetivos destacar os principais aspectos etiopatogênicos do vitiligo, bem como, apresentar as opções terapêuticas atuais para o manejo da doença. *Método*: Revisão bibliográfica narrativa, utilizando-se as bases de dados Pubmed (US National Library of Medicine) e Portal Capes. A busca dos trabalhos foi realizada no ano de 2018, utilizando-se os seguintes Descritores em Ciências da Saúde: *Vitiligo; Autoimunidade; Repigmentação; Tratamento Farmacológico; Fototerapia; Cosméticos; Cirurgia; Enxerto de tecido*. Foram selecionados 26 artigos publicados no período de 2011 a 2018 que apresentaram conteúdos relacionados aos objetivos deste estudo. *Resultados*: O vitiligo desenvolve-se pela associação da predisposição genética e exposição a fatores ambientais. O tratamento tem o objetivo de limitar a progressão da doença, promover repigmentação das áreas afetadas e prevenir recidivas; podendo ser dividido em clínico, estético e cirúrgico. Os medicamentos tópicos, os sistêmicos, a fototerapia e os recentes imunobiológicos constituem tratamentos clínicos. O tratamento estético é representado pela camuflagem cosmética e o cirúrgico é indicado para aqueles que apresentam doença estável não responsiva a terapia clínica. *Conclusão*: O tratamento em geral é realizado pela associação de terapias, razão pela qual deve ser individualizado para cada paciente. O início precoce do tratamento está associado a um prognóstico mais favorável. Torna-se de extrema importância não negligenciá-lo além de conhecer inovações terapêuticas, tendo em vista o potencial estigmatizante da doença; melhorando assim a prática clínica e a qualidade de vida dos pacientes.

Descritores: Vitiligo; Autoimunidade; Repigmentação; Tratamento Farmacológico; Fototerapia; Cosméticos; Cirurgia; Enxerto de tecido.

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INTRODUCTION

Vitiligo is a chronic autoimmune skin disease that is considered the most common depigmentary disorder of the skin[1]. It is a condition that leads to loss of pigmentation, histologically characterized by the absence or inactivity of epidermal melanocytes[2]. It affects approximately 0.5% of the world population. In Brazil, this disease affects 1.2% of white people and 1.9% of brown/black people and is among the 25 most frequent dermatological diseases in all the macro-regions of the country[3]. Both genders are equally affected, and there is no difference in relation to skin color and race. It can develop at any age; however, in most patients, symptoms start before they reach 20 years old[2].

The pathogenesis of this disease is multifactorial and includes factors such as genetic predisposition, environmental factors, oxidative stress and immunological changes[4]. It is classified as segmental and non-segmental, according to its location on the skin and its progression[1].

Treatment for vitiligo includes clinical, aesthetic and surgical therapies to contain the progression of the disease, stimulate the repigmentation of the skin and prevent recurrences[5]. The clinical treatment of patients includes several therapeutic options, such as topical medications, oral corticosteroids, immunobiologicals and phototherapy[6]. The choice of the best treatment approach depends on the extent of the lesions and the stability of the disease. The aesthetic treatment of cosmetic camouflage is complementary to other treatments and has the objective of improving the quality of life of patients[5]. Surgical treatment is indicated for stable vitiligo that does not respond to clinical treatment. Among the surgical treatments, transplantation of melanocytes is one that has gained popularity in recent years[7].

Understanding the pathogenesis of vitiligo, the available and emerging treatments and their contribution to self-esteem and to the patient's quality of life is essential to improve the management of this pathology. Therefore, this study addresses the main etiopathogenic mechanisms of vitiligo and presents the current treatment options that are available and effective for this pathology.

METHOD

This is a narrative literature review, using the electronic databases Pubmed (US National Library of Medicine) and *Portal CAPES*. The search for studies was carried out from January to December 2018. Articles in Portuguese and English were selected using the following Health Sciences Descriptors, either alone or combined*: Vitiligo; Autoimmunity; Repigmentation; Drug Therapy; Phototherapy; Cosmetics; Surgery; Skin Grafting*. Articles published between 2011 and 2018 were evaluated and selected. The main focus of this study was the current treatments available for vitiligo. Among the search results, 26 articles that contributed to the objectives, relevance and currency of the present study were selected. In this search, studies published before 2011, duplicate and/or unavailable studies, and studies that did not address the topic under study were excluded.

RESULTS

The search in the databases returned a total of 98 articles. Of these, 03 were duplicates, 49 were excluded after analysis of the abstract and full-text, and 20 did not have the full text available. At the end of the exclusions, 26 articles were included in this study.

This review narrates the main etiopathogenic and clinical aspects of the disease and the current therapeutic possibilities for the proper management of patients with vitiligo, according to evidence found in individual studies.

DISCUSSION

Etiopathogenesis of Vitiligo

Due to multiple factors and genes involved, the etiology of vitiligo is quite complex, and many aspects remain to be unveiled. Genetic predisposition is one of the factors involved in the genesis of the disease. First-grade relatives have a 6-8% risk of developing vitiligo, and the concordance of vitiligo in monozygotic twins is approximately 23%[2]. The candidate genes associated with the disease are HLA, AIRE, VIT1, CAT, FOXD3, ESR1, COMT, PTPN22, NALP1, PDGFRA, MYG1, MITF, CD117, XBP1, FAS, COX2, EDN1 and ACE; which can be located on several chromosomes, including chromosomes 1, 2, 4, 6, 7, 8, 9, 14, 17, 19, 21 and 22[2].

Studies suggest that melanocytes from vitiligo patients have intrinsic defects that reduce their capacity to manage cellular stress, making them more vulnerable to constant stressors such as ultraviolet radiation and various chemicals[4, 8].

In the pathogenesis of vitiligo, autoimmune, genetic and environmental factors act in combination, leading to the absence of melanin in the areas affected. These factors lead to altered immunity and induce the production of autoantibodies and activation of CD8 + T lymphocytes, which lead to the destruction of melanocytes[8,9]. The environmental factors mentioned most often in the literature are hormonal changes, traumas, psychological stress, puberty, pregnancy, diet and changes in lifestyle[9].

Classification

Vitiligo can be classified as segmental and non-segmental, depending on its location on the skin. Non-segmental vitiligo affects 85 to 90% of patients and is characterized by the presence of white macules involving

multiple parts of the body bilaterally, most often in a symmetrical pattern[1]. It has a chronic course, with a continuous progression of lesions throughout life[2].

Segmental vitiligo affects 10 to 15% of patients and is characterized by depigmentation on one side of the body, usually respecting the midline[1]. This form of the disease has a rapid onset, varying from days to weeks, and usually stabilizes after 1–2 years [2].

Psychosomatic aspects of vitiligo

The stigma of the disease usually causes patients with vitiligo to have a negative self-image and low self-esteem, which leads to impairment of social life, especially for females and adolescents/young adults[10].

A study showed that 88% of patients affected by the disease expressed psychological complaints, such as fear that the spots will spread (71%), shame (57%), insecurity (55%), sadness (55%), inhibition (53%), displeasure (50%), impatience (43%), irritability (36%), unhappiness (35%), negative image to others (35%), anger (26%), bitterness (25%), lack of self-confidence (25%), being disgusted with yourself (18%) and others (16%)[11].

The literature shows a high association between vitiligo and the development of psychiatric diseases, especially depression. Psychiatric morbidity affects 35% of patients in the United Kingdom and 25% in India. In addition, approximately 25% of patients report that vitiligo directly interferes with their sexual activities and affective relationships[11].

Therefore, the treatment of lesions directly affects the quality of life of these patients, in the various aspects of relationships and even in their professional lives[10].

Clinical treatment

Treatment options include topical drugs, oral drugs and phototherapy, however, none of these treatments cure the disease[6]. Topical agents and phototherapy with Excimer Laser are recommended for segmental vitiligo, which affects small areas of the body. Phototherapy with the Psoralen Plus Ultraviolet A (PUVA) and Narrowband Ultraviolet B (NB-UVB) is indicated for generalized vitiligo[6].

Pharmacological treatment with topical drugs

Topical calcineurin inhibitors such as Tracrolimus and Pimecrolimus, can be used as first-line topical treatment for segmental vitiligo[7]. Repigmentation occurs mainly due to the inhibitory mechanism of T lymphocyte activation, which has a direct effect on melanocyte migration and differentiation during repigmentation[12]. Studies suggest that the combination of tacrolimus with NB-UVB phototherapy or with Excimer laser presented better results when compared to use of phototherapy alone[13].

Topical corticosteroids such as Clobetasol are also useful in the treatment of small lesions of segmental vitiligo, acting in the differentiation of melanocytes[12]. They present some side effects such as epidermal atrophy, steroid-induced acne, rosacea, telangiectasia, ecchymoses and striae. Patients treated with more potent corticosteroids have a higher risk of atrophy[5]. Thus, lesions located in the face, neck and intertriginous areas should be treated with midpotency corticosteroids; lesions in the rest of the body can be treated with ultrapotent corticosteroids[7].

Vitamin D analogues can also be used in the treatment of vitiligo, as they inhibit T-cell activation; however, they have no relevant effect on repigmentation when used alone[12]. The therapeutic effect of these drug is obtained in combination with phototherapy or with topical corticosteroids[12].

Pharmacological treatment with systemic drugs

Oral corticosteroids are effective in the treatment of vitiligo because they can help stabilizing the disease. They are also indicated for progressive vitiligo, with the objective of reducing autoimmune destruction of melanocytes[7]. They have several side effects, including weight gain, insomnia, acne, menstrual irregularities and hypertrichosis[7]. Reports of discontinuation of treatment due to side effects are common[5].

Immunobiologicals – blocking of interleukin 17 (IL-17A) and its receptor in melanocytes

Studies point to the important role of IL-17, a pro-inflammatory chemokine, in the onset of inflammatory autoimmune diseases. In vitiligo, the increased expression of this chemokine can modulate the growth, maintenance and production of melanocytes, inducing depigmentation by acting in the down-regulation of the genes involved[14].

The neutralization of IL-17 or its receptors with monoclonal antibodies reverses the blockade effect of melanogenesis. IL-17A blocking results in the prevention of cell death as well as expression of genes required for melanocytes survival, restoring melanin production[15]. Among the immunobiological IL-17 inhibitors are secukinumab, ixekizumab and brodalumab. Secukinumab and ixekizumab are antibodies that target IL-17A itself, while brodalumab acts by binding to the IL-17A receptor (IL-17RA) and blocking the actions of this chemokine[14,15].

This suggested a promising strategy against melanocytes loss in vitiligo, using systemic biological therapies that target specific chemokines in the course of the disease[15].

Janus Kinase Inhibition

Janus Kinase (JAK) participates in the process of transcription and translocation of genes involved in skin

depigmentation[16]. These genes depend on IFN-γ, as the binding of IFN-γ to its receptor activates the JAK pathway and leads to the secretion of cytokines such as CXCL9 and CXCL1 to the skin. These cytokines are responsible for the recruitment of autoreactive CD8 + T cells that attack melanocytes and lead to depigmentation[16]. As a therapeutic option to inhibit this process, tofacitinib and ruxolitinib act as JAK signaling inhibitors, blocking the recruitment and destruction of melanocytes[16].

Areas exposed to the sun obtained a better response with the use of this treatment, since pigmentation depends on photoactivation, which stimulates melanocytes to migrate to the epidermis[17].

Phototherapy

Psoralen Plus Ultraviolet A (PUVA) was the first method of phototherapy used to treat vitiligo. This method begins with the intake of photosensitizing medication; then, the patient is exposed to UVA irradiation with wavelengths from 320 nm to 400 nm[18]. It has side effects such as nausea and vomiting and is associated with an increased risk of developing skin cancer[19].

For this reason, this technique is being gradually replaced by Narrowband Ultraviolet B (NB-UVB), which has fewer adverse effects and greater efficiency[18]. A study found that the overall treatment response to NBUVB phototherapy was better than to PUVA therapy[6]. Today, NB-UVB is considered the first-line choice for the clinical treatment of generalized vitiligo[20].

NB-UVB phototherapy is characterized by polychromatic light with a peak emission wavelength of 311 to 313 nm. In stable vitiligo, it has a lesion repigmentation effect due to stimulation of functional melanocytes in the perilesional skin or immature melanocytes in hair follicles[18]. In unstable vitiligo, it acts by inhibiting the activity of autoreactive T lymphocytes, reducing the disease progression[18].

Treatment with NB-UVB in combination with topical calcineurin inhibitor, topical vitamin D analogues and other therapies has shown good results, synergistically improving the efficacy and shortening the duration of phototherapy[20].

Excimer Laser with a wavelength of 308 nm is currently considered an effective method for the treatment of localized vitiligo[5]. Laser acts on repigmentation by inducing apoptosis of T cells and stimulating the proliferation and migration of immature melanocytes[18]. It allows the application of high-intensity radiation to specific areas of the skin, sparing the surface that does not have hypopigmentation, and thus preventing the hyperpigmentation of healthy perilesional skin[21].

Aesthetic treatment – cosmetic camouflage

Cosmetic camouflage refers to the technique in which creams, foundations, concealers and other cosmetics are used to temporarily or permanently repigment areas affected by vitiligo. It is currently used to cover scars, imperfections and pigmentary abnormalities, including vitiligo[22].

Camouflage techniques can be especially useful in patients who do not achieve complete or immediate results with other types of treatment, such as clinical and surgical treatment. It is a more accessible, simple, non-invasive and easily reproducible technique with immediate result, and it does not intend to replace other forms of treatment, but to complement them. In these cases, corrective makeup can be of great importance to minimize the impact of this skin condition on the quality of life of patients[23].

A study by Padilla-España et al. (2014) evaluated the positive impact of treatment with cosmetic camouflage on the quality of life of patients using the Children Dermatology Quality Index (cDLQI). After treatment sessions for both practical and didactic purposes, the questionnaire was reapplied and showed a significant improvement in the participants' quality of life[10].

Types of camouflage

Foundation coverage

These are the most common and best products available for camouflage purposes. Products typically contain up to 25% more pigment compared to normal makeup, are waterproof and require a single daily application[22]. The primary emulsifier is usually triethanolamine or a non-ionic surfactant and the secondary emulsifier is usually glyceryl stearate or propylene glycol stearate. Limitations of this type of camouflage include difficulty to apply over larger surface area, high cost and restricted use in patients with acne or other injuries[22].

Self-tanning products

Self-tanning products have been used effectively for the camouflage of vitiligo lesions. The most common products have Dihydroxyacetone (DHA) as active principle. DHA reacts with proteins in the stratum corneum to form the so-called melanoidins, which will give the skin the desired color, which lasts about 10 days. The concentration of DHA required is higher in people with darker skin[22].

DHA also has sun-screening properties, but they are low compared to the recommended protection and tend to decrease with each day after application. Its disadvantages include the difficulty in obtaining the desired color and blending it with the surrounding skin and the possibility of causing allergies and dermatitis, DNA damage and mutagenic effect on keratinocytes[22].

Micropigmentation

Micropigmentation, dermatography or medical

tattooing is a tattoo for cosmetic and medicinal purposes that ensures permanent camouflage in a wide range of dermatological diseases. It is also widely used as a finishing step in craniofacial surgeries and breast reconstruction[22].

The procedure is associated with high patient satisfaction and low complication rates, and it has better results in darker skin. It is indicated when vitiligo is resistant to other treatments, stable and localized[22].

Some of the advantages of this treatment modality are the quick and instantaneous result, the relatively low cost and the possibility of using it in the eyelid area, where other methods can not be used. Disadvantages and limitations include difficulty in getting an exact color match, gradual fading, contact allergies and the risk of transmission of infective diseases. Immediate adverse effects usually result from improper technique and lack of adherence to asepsis. These include bruises, crusts, edema and secondary bacterial infection[22].

Surgical treatment

The surgical treatment of vitiligo was first reported in 1947 and, since then, surgical techniques have become more sophisticated and varied[24].

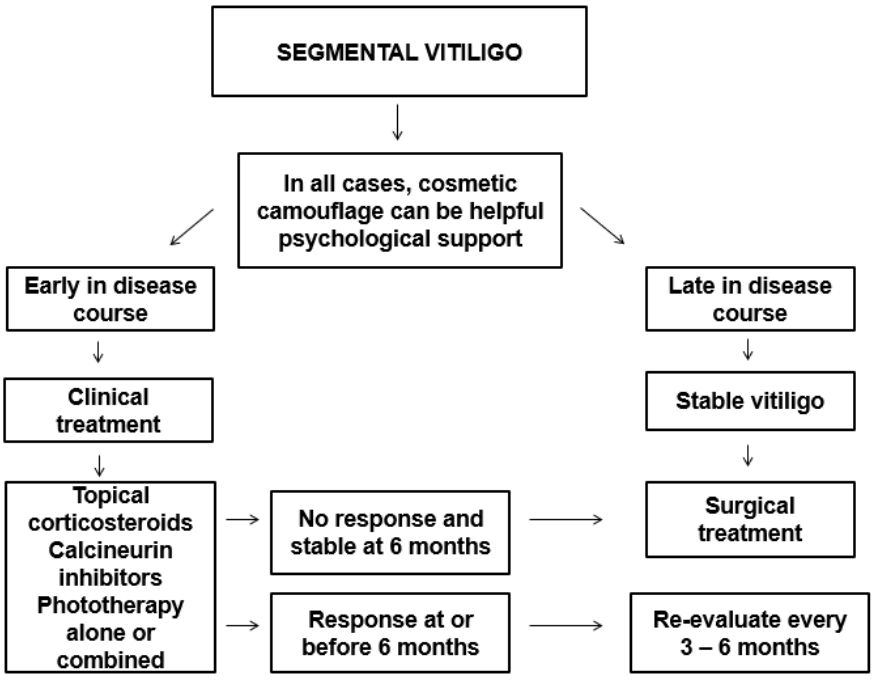
Surgery is indicated for patients with a stable disease; stability of vitiligo is defined by the absence of new lesions over 6 months to 2 years[7]. Patients with segmental vitiligo are the ones that most benefit from surgical intervention and have an extremely favorable response. Lesions in areas of the body with a greater vascular supply and follicular density, such as head and neck, have a better response to surgery than lesions in extremities[24].

Surgical options can be divided into tissue grafting methods and cellular grafting methods[25]. Tissue grafting involve the transfer of tissue from the own patient to the lesion site and are ideal for treating small areas[24]. It has the advantages of being a low-cost procedure that does not require sophisticated equipment, has good efficacy and provides uniform color match and low rates of scarring[7].

Cellular grafts involve creating a cellular suspension from a thin to ultrathin skin graft[24]. Today, noncultured epidermal suspension, also known as melanocyte transplant, is performed more frequently and is considered the gold standard for vitiligo grafting[7].

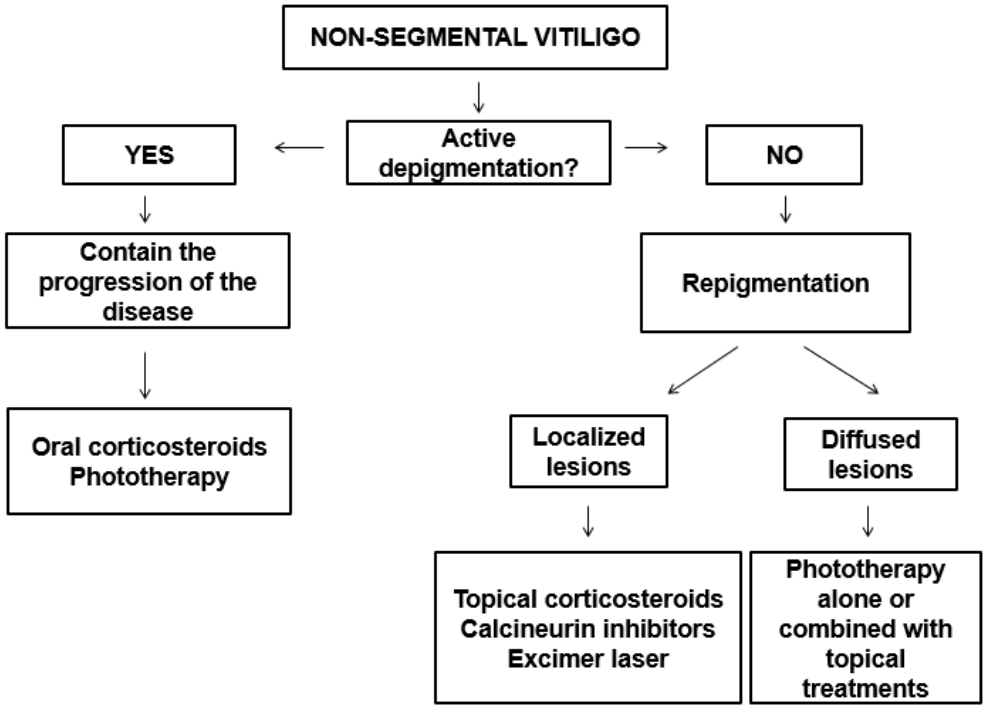
The melanocyte transplant procedure starts with obtaining a skin sample from a normally pigmented area; the scalp, gluteal region and thigh are often used in this step[25]. The sample is immersed in trypsin-ethylenediaminetetraacetic acid (EDTA) and then incubated for a period of 60 minutes. Then, the epidermis is separated, centrifuged and suspended in solution to isolate a sample of cellular suspension containing melanocytes and keratinocytes[25]. It is necessary to prepare the recipient area, through dermabrasion down to the dermo-epidermal junction. Then, a syringe is used to apply cell suspension on the denuded area. The area is covered with collagen and a dressing, which remains for 4–7 days[26].

A treatment algorithm for vitiligo is illustrated in Figures 1 and 2.



Source: Adapted from Passeron[5], Rodrigues[7]

Figure 1: Treatment algorithm for segmental vitiligo



Source: Adapted from Passeron[5], Rodrigues[7].

Figure 2: Treatment algorithm for segmental vitiligo

CONCLUSION

There are several treatments that are available and effective for vitiligo, encompassing clinical, aesthetic and surgical treatments. Among these, there are innovative and promising therapies, such as the use of immunobiologicals, which act by inhibiting specific mediators in the genesis of the disease, and melanocyte transplant, a cell suspension graft that acts in the repigmentation of the affected area.

So far there is no cure for vitiligo and no effective method to contain the spread of the disease. The treatment, which is sometimes unsatisfactory, aims to control the inflammatory/autoimmune process and stimulate skin repigmentation.

Properly applied camouflage techniques can improve the appearance of lesions considerably, increasing self-esteem and quality of life.

The association between these treatments is necessary, since it leads to optimized outcome of the lesions and greater patient satisfaction. Studies highlight that combined treatments offer a greater chance of successful repigmentation.

In general, treatment is long, which is why the patient must be individually evaluated and the risks and benefits of each therapeutic option must be considered, minimizing their side effects.

Because there is no loss of functional capacity, vitiligo is approached by many professionals as something solely aesthetic. Awareness about the importance of early diagnosis and about new treatment approaches for this condition is extremely important, especially considering the stigma of the disease and the social and psychological damage it causes in the patients affected. With this, it is possible to improve care, clinical practice and quality of life of patients with this disease.

Authors participation: *Mendonça AEA* and *Aquino DD*: Conception of the study, research and data collection, analysis and interpretation, writing of the manuscript, critical review of the manuscript. *Sobrinho HMR* and *Horbilon JAM*: Guidance, conception of the study, research and data collection, analysis and interpretation, writing of the manuscript, critical review of the manuscript.

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Received: March 29, 2019
Accepted: March 17, 2020