Scientific Electronic Archives (7): 111-120, 2014.

Immunopathology of Vitiligo: A Review of Literature

A. E. Silva [1], L. Castoldi [1+]

[1] Universidade Federal de Mato Grosso – Campus Sinop

[+] Address for correspondence: lindseycastoldi@gmail.com

Abstract

Vitiligo is a morbidity characterized by depigmentation of body parts from the loss or reduction of melanocytes. The disease affects an average of 1% of the world population, usually individuals with mean age of 20, affecting both men and women regardless of race. Within existing therapies, there are many treatments being offered, however, improvements upon treatments vary from person to person and cure is rare to obtain. The etiology of vitiligo is still not clear, there are many hypothesis for his cause. Then, this study aimed to review literature regarding the latest immunological mechanisms involved in the onset of vitiligo.

Keywords: *vitiligo; immunopathology, autoimunnity.*

Brackground

Vitiligo is a skin disorder that affects about 1 to 2% of people in the world (Barros et al., 2007), affecting individuals of all races, ages and gender. The onset of the disease occurs mostly between twenty and thirty years, and heredity seems to be an important factor, since about 38% of patients have close relatives with the disease (Nunes & Esser, 2011; Bassiouny & Shaker, 2010).

Vitiligo is a dyschromia characterized by lesions of depigmentation resulting from loss of epidermal melanocytes (Nai et al., 2008; Boorn et al., 2009), cells responsible for the production of melanin which gives the skin pigmentation, body hair and eyes (Nai et al., 2008; Boorn et al., 2009).

The disease is classified according to the regions affected by the lesions and the extent of depigmentation. The lesions can therefore be localized, the focal type i.e. which is characterized by the presence of one or more macules in a specific area, without a particular distribution; segmental, when macules are localized in specific epidermal area and mucosal, when only the mucosa is affected (Nunes & Esser, 2011). The generalized form presents the acrofacial type where the macules appear in the distant extremities and facial area location, vulgar type, where amelanotic lesions have an irregular distribution, and mixed, when there are two or more types of classification for the disease (Nunes & Esser, 2011). The universal vitiligo is one in which depigmentation occurs in 50% of the mucous membranes and/or the epidermis (Nunes & Esser, 2011). A study on the epidemiological profile of patients with vitiligo by Nunes & Esser (2011), demonstrated the generalized form of the ordinary type as being the most prevalent form, reaching 70% of the 69 patients that participated in the survey, followed by the focal type, universal, acrofacial and segmental.

The physical locations most affected in patients include the face, extremities and acral regions in general (Speeckaert & Geel, 2013). However, in women, areas such as the trunk, hips, groin, armpits, arms, elbows and feet are most affected compared to men, who in turn presents depigmentation usually common close to the beards and genital areas (Speeckaert & Geel, 2013). Young people (<20 years) are more susceptible to vitiligo in the lower extremities, as in older people, the macules are preferentially located in the upper extremities, indicating pathological forms in accordance with the clinical aspects (Speeckaert & Geel, 2013).

Diagnosis and classification of vitiligo are performed by clinical history and evolution of disease after checking local depigmentation with Wood's light (Nai et al., 2008). Other methods, such as biopsy and immunohistochemistry are used when there is need for differential identification of other depigmentation pathologies (Nai et al., 2008).

The mark of vitiligo is loss of melanocytes resulting in the reduction or absence of melanin, however, other disorders can also be viewed as interface dermatitis, such changes are seen mainly in stable vitiligo (Nai et al., 2008).

Although many researchers have reinforce the hypothesis that melanocytes are present in vitiligo but without the ability to produce melanin, immunohistochemistry and electron microscopy studies have confirmed the total disappearance of these cells in the damaged areas (Machado Filho et al., 2005; Souza Filho et al., 2005; Montes et al., 2003).

Several existing treatments are in search of stabilization or even cure of vitiligo, considering the classification of patches, if the disease is active or stable and the affected site (Hartmann et al., 2004). Most treatments use tissue abrasion injuries in an attempt to stimulate the inactive melanocytes in inducing repigmentation process, however the exact response of melanocytes to these techniques is not known (Machado Filho et al., 2005; Parsad et al., 2004; Barros et al., 2007).

Phototherapy is another form of treatment which is widely used in the modulation of immune responses that

involve the skin, acting on Langerhans cells and keratinocytes, when it comes to UVB irradiation (Casara et al., 2013). Phototherapy with UVA main to act on dermal fibroblasts, mast cells, endothelial cells, lymphocytes and granulocytes T, producing excellent results on the face and trunk of affected individuals (Casara et al., 2013).

The steroids are options available to patients with stable vitiligo. Corticosteroids may be used for their immunosuppressive, anti-inflammatory and stimulation of repigmentation action (Saldanha et al., 2012). Treatment with oral corticosteroids is used in cases of extensive or progression vitiligo and topically treatment is selected for stabilization and repigmentation of areas difficult such as hands and fingers (Saldanha et al., 2012).

Surgical grafting techniques have long been used as other forms of treatments especially in patients with at least one year of stable vitiligo and who have not responded well to other treatment techniques (Saldanha et al., 2012). The main surgical grafting techniques are micro-punch through the graft by suction blister, the skin graft obtained by dermatome, and the suspension culture of epidermal cells which are based on the implantation of melanocytes from skin areas of healthy depigmented areas (Saldanha et al., 2012). In some cases, the phenomenon called satellite repigmentation, in which areas of melanin pigmentations appear in peripheral areas of the graft can occur, which may be a consequence of the action of keratinocytes of the graft developing/inducing growth factors to the melanocytes of transplanted area, which multiply and migrate to the achromatic lesions or by the growth factors present in vitiligo lessions responsible for making the melanocytes inactive (Saldanha et al., 2012). Makeups and tanning can be used to cover and disguise patches.

The acral regions (wrist, ankle, hands, feet) when affected have greater difficulty of clinical and surgical treatments because it respond inappropriately (Holla et al., 2013). Possibly, this characteristic is due to factors such as frequent movement of these sites, which could lead to loss of melanocytes deployed, or even because they have less connective tissue that can enabled infiltration of the melanocytes from the grafts (Holla et al., 2013).

Furthermore, lesions at the joint and acral regions are very common due to frequent exposure to trauma which may result in Koebner phenomenon in which small or large injury may lead to loss of melanocytes in the injured area, causing the whitish blotches (Holla et al., 2013; Speeckaert & Geel, 2013). These areas treated may suffer with the marginal repigmentation, which is a hyperpigmented lesion in the periphery and the central region turns red/pink, without central pigmentation (Holla et al., 2013; Speeckaert & Geel, 2013).

The emotional aspect is of great relevance for the emergence or increase of vitiligo (Souza et al., 2005). Victims of vitiligo cited loss or detachment of close person as a leading factor in the emergence of the disease (Souza et al., 2005). The loss of close relatives or personalities considered of extreme importance can result in severe stressful events which depending on how they are experienced (personality), may result in immunological changes and the triggering of psycodermatoses (Souza et al., 2005). Thus, patients who received multidisciplinary treatments including medical and psychological follow-ups presented improvements in repigmentation than those accompanied only by medical treatments.

Vitiligo as an autoimmune disease

There are several hypotheses suggesting the etiology of vitiligo. Among the principal hypotheses is the neural, which states that the accumulation of toxic substances at the nerve endings damage the melanocytes and consequently decreases the production of melanin; biochemical hypothesis implies that the accumulation of toxic products from

melanotic synthesis, damaging the melanocytes and the autoimmune hypothesis, the target of this work, defended by its frequent association with autoimmune diseases and reports based on the identification of antibodies and autoreactive lymphocytes against melanocytic antigens (Kemp, 2004). Besides these, other causes of depigmentation in vitiligo that have been cited are stress, infections and genetic factors (Kemp, 2004). In fact, these proposed aetiologies can act independently or in combination, the latter makes up the convergence theory in which all aetiologies act with the same objective: the destruction of melanocytes or different pathogenic aetiologies could justify the different types of vitiligo: a neural hypothesis is associated with segmental vitiligo type, while the autoimmune becomes involved with the generalized form (Kemp, 2004).

The immunological hypothesis is strengthened by the co-existence of vitiligo with autoimmune diseases in many patients, such as type I diabetes mellitus, multiple sclerosis, Addison's disease, pernicious anemia, alopecia areata, rheumatoid arthritis, Sjogren's syndrome, Hashimoto's thyroid, chronic mucocutaneous candidiasis and the ability of melanocyte to stimulate autoantibodies production, which act by combating antigens located on the melanocytes surface (Budel et al., 2006). The amount of circulating autoantibodies to melanomas antigens is associated with the lesion area and activity of the disease, further supporting the autoimmune hypothesis (Budel et al., 2006). Furthermore, immunosuppressive treatments enables improvement repigmentation in most patients by contributing to the blocking of melanocytes lysis by cytotoxic antibodies or the induction of apoptosis by T cells infiltrating the skin, in addition to other immunosuppressive activities (Machado Filho et al., 2005; Budel et al., 2006).

The presence of organ-specific antibodies (e.g., thyroid or adrenal) is related to the duration of the disease, but not with the clinical aspects of vitiligo because it is not able to explain the lesions directed to melanocytes and in an indescribable manner, the disease often precedes autoimmune disorders, thereby requiring assessment of target organs in patients with vitiligo (Ongenae et al., 2003). Autoimmune thyroiditis is the most frequent disease in patients with vitiligo (30%), being a higher percentage when compared to individuals in general (1%) according to the Brazilian Society of Information of Medical Pathology (Budel et al., 2006).

Geel et al. (2013) observed that autoimmune diseases present in patients with vitiligo can somehow induce clinical delineation in individuals with generalized vitiligo; an example of this is the observation of body areas flagging the loss of melanocytes in patients with thyroid disorders. In addition, people who suffer from other autoimmune diseases, other than the thyroid, the sites of frequent friction as elbows, knees, hands, ankles and feet are less impaired compared to patients with thyroid diseases, thus tracing part of a clinical profile (Geel et al., 2013).

In most patients autoantibodies that also act against the melanocytes are found, and considering that these skin cells are found in other regions such as eyes, inner ear and meninges, it is evident that patients with vitiligo may have other physical functions affected (Gopal et al., 2007). The participation of these antibodies in the lysis of melanocytes was demonstrated in recent studies in which sera from patients with vitiligo was toxic for melanoma cells, inducing tumour remission (Budel et al., 2006).

The tegumentary system often develops immune response in which cytotoxic specific $CD8^+$T cells eventually injured skin cells. Various studies have shown the presence of CLA^+CD8^+T lymphocytes specific to melanocytes in the regions near the lesions, demonstrating immunological involvement in the pathogenesis of vitiligo (Antelo et al., 2008).

Thus, the various hypotheses combine to cause damage to the skin leading to melanotic disorder, and subsequently vitiligo (Antelo et al., 2008a; Souza Filho et al., 2005).

Humoral Immunity

Patients with vitiligo have a range of circulating autoantibodies against melanocytic antigens and other tissues, whereas such antibodies are not found in patients with other diseases (Gopal et al., 2007). Although some antibodies are specific for antigens expressed on non-pigmented cells, the disease affects more sharply the skin, which may be related to increased sensitivity of melanocytes to immune reactions than other cells or due to the destruction of melanocytes affecting other target sites, not limited to the epidermis (Gopal et al., 2007). It is possible that these antibodies are not specific for vitiligo etiology, but may only act on already damaged melanocytes, however, the amount of anti-melanocyte antibodies has been correlated with the intensity and extent of the disease (Kemp, 2004).

In order to observe the involvement of antibodies to combat melanocytic antigens, a fragment of human skin was grafted on mice animals, and subsequently inoculated with purified IgG from patients with vitiligo (Farrokhi et al., 2005). It was possible to identify that the quantities of immunoglobulins infused reconciled with the extinction of the melanocytes (Farrokhi et al., 2005). This *in vivo* analysis placed greater emphasis on the effect of autoantibodies on the melanocytes lysis (Farrokhi et al., 2005).

Several studies have shown that autoantibodies belong to the IgG class. The purified IgG derived from patients with vitiligo have the ability to lyse melanoma cells (Kemp, 2004). In addition, reports indicate increased levels of IgG according to the intensity and extent of the disease, but other studies suggest IgA as an inherent vitiligo antibody (Kemp, 2004). The tyrosinase related proteins, TRP-1 and TRP-2, are considered melanocytic antigens, since they are expressed in the cell membranes, allowing their destruction (Souza Filho et al., 2005; Mandelcorn-Monson et al., 2003). The gp100, MelanA/MART1 (melanosomal autoantigen) and MCHR1 (melanin-concentrating hormone receptor-1) are also observed in patients with vitiligo (Souza Filho et al., 2005; Mandelcorn-Monson et al., 2003).

Relatives of vitiligo patients have a high concentration of serum autoantibodies, indicating the importance of the relationship of family history and vitiligo, as the disease is inherited as a polygenic attribute (Mandelcorn-Monson et al., 2003). Fifteen of the 16 genes implicated in recent genome-wide association studies are involved in immune response pathways, including genes localized to the major histocompatibility complex (MHC) loci and regulators of the innate immune system (Manga & Orlow, 2012; Yamaguchi & Hearing, 2014).

In addition to the anti-melanocyte antibodies, humoral immunity is supported by association with autoimmune endocrine diseases such as type I diabetes mellitus, multiple sclerosis, Addison's disease, pernicious anemia, alopecia areata, rheumatoid arthritis, Sjogren's syndrome, Hashimoto's thyroid, chronic mucocutaneous candidiasis and systemic lupus erythematosus (Budel et al., 2006; Bassiouny & Shaker, 2010).

The prevalence of autoantibodies, including thyroid antibodies increases the emphasis of immunity as a major factor in the etiology of vitiligo (Daneshpazhooh et al., 2006). The presence of autoimmune diseases and organ-specific antibodies are reported in vitiligo, mainly thyroiditis (Daneshpazhooh et al., 2006). Studies indicate the presence of anti-TPO (thyroid peroxidise antibody) in higher levels in patients with vitiligo compared to people who do not suffer from the disease, especially in the young women subjects, however, these antibodies may represent markers of vitiligo and may not be involved in the disease pathogenesis (Daneshpazhooh et al., 2006).

Studies have shown increased antigens of melanocytes in active lesions of patients with melanoma and consequent destruction of melanocytes (Singh et al.,2006).

Therefore, these antigens can be expressed more preferably in melanocytes or the response of immune cells occurs after the death of melanocytes resulting from other mechanisms.

Cellular Immunity

The first indication of involvement of cellular immunity in vitiligo arouse from the discovery of infiltrating T cells in the margins of perilesional vitiligo (Bassiouny & Shaker, 2010).

Recent studies highlight the participation of cytotoxic $CD8^+/CLA^+$T cells in the destruction of pigment cells (Antelo et al., 2008). The cutaneous lymphocyte antigen (CLA) is one of those responsible for the arrival of lymphocytes to the skin, thus reducing the CLA expressed by lymphocytes may indicate a treatment option for diseases involving such lymphocytes (Antelo et al., 2008).

Antelo et al. (2008) noted that PUVA treatment (UVA radiation) reduced by 25% the number of CLA^+ $CD8^+$T lymphocytes, CD4/CD8 ratio reducing to near-normal values, with improvement of clinical lesions in a patient with generalized vitiligo.

Dwived et al. (2013) observed that $CD8^+$ T cells are found in abundance in patients with generalized vitiligo compared to controls, whereas $CD4^+$ T cells do not express significant changes in carriers of the disease and in controls. Comparing patients with active and stable disease, the $CD8^+$ T cells were elevated in active vitiligo, whereas there was no difference in the $TCD4^+$ cells, indicating the importance of $CD8^+$ T cells in the course of the disease (Dwived et al., 2013). There is no difference in T cell counts between men and women and between young or the old people (Dwived et al., 2013). Regulatory T cells (Treg) are also present in smaller amounts in active vitiligo in relation to the stable and in patients compared to controls, indicating an immune imbalance and perhaps not controlling the activation of $CD8^+$ T cells, leading to the destruction of melanocytes (Dwived et al., 2013).

Studies have shown $CD8^+$ T lymphocytes specific for Melan-A in the serum of patients with vitiligo, clearly evidencing involvement of cellular immunity dependent on $CD8^+$ T lymphocytes (Antelo et al., 2008). The interleukins (IL) -2, IL-6 and IL-8 have been found in increased levels in patients with the disease, further strengthening the opinion that T cells is involved in the etiopathology of vitiligo (Mandelcorn-Monson et al., 2003).

Mandelcorn-Monson et al. (2003) demonstrated that 88% of patients HLA-2 (human leucocyte antigen) have Tc lymphocytes specific for gp-100, being absent Tc lymphocytes specific for MelanA/MART-1 and tyrosinase. Thus, the recognition of gp100 by immune cells in patients with vitiligo in active stage can be associated with the activity of the disease since the activity of immune cells is low in patients with the disease in the stable phase (Mandelcorn-Monson et al., 2003).

Boorn et al. (2009) observed lymphocytic infiltrates in the perilesional region of vitiligo substantiating the destruction of melanocytes by Tc cells. Furthermore, the presence of specific T cells was also observed in the circulation (Boorn et al., 2009). In this study, $CD4^+/CD8^-$ Tcells of the patients were able to produce cytokines such as tumor necrosis factor–alfa (TNF-a), interferon (IFN), IL-4 and IL-17 (Boorn et al., 2009). Beyond melanocytes, keratinocytes affected also undergo apoptosis and thus the epidermal structure was reached (Boorn et al., 2009).

Nai et al. (2008) in their study on the early diagnosis of vitiligo by immunohistochemistry, reported lymphocytic infiltrates in lesions of individuals with recent clinical manifestations and increased Langerhans cells in the damaged epidermis. The expression of MHC class II is present in greater quantities in perilesional

melanocytes compared to melanocytes elsewhere (Souza Filho et al., 2005).

According to Esmaeili et al. (2011) cytokines are involved in the pathogenesis of vitiligo, including IL-17, which is produced by Th17 cells, is responsible for driving many pro-inflammatory mediators such as cyclooxygenase-2 (COX-2). In this study there was no significant expression of IL-17 and COX-2 in lymphocytes, however, these mediators showed an increase in neutrophils as analyzed suggesting that there is an involvement of IL-17 and COX-2 in inflammation in patients with vitiligo (Esmaeili et al., 2011). Bassiouny & Shaker (2010) corroborate these findings by demonstrating increased IL-17 in diseased skin and in serum of patients with vitiligo.

By assessing the level of IL-17 in serum of patients with vitiligo, an inverse relationship between cytokine levels and the time of onset was observed, with the concentration being associated with the affected body parts (Basak et al., 2009).

Th1, Th2, Treg and Th17 cells are $CD4^+$T cell subsets that secrete cytokines and are involved in many autoimmune diseases including vitiligo (Tembhre et al., 2013). Tembhre et al. (2013) reported high levels of IL-10, IL-13 and IL-17 Th and reduction of transforming growth factor beta (TGF-β)1 in serum, supporting the idea of altered cellular immunity as part of the etiology of vitiligo. The presence of higher levels of IL-6 and TNF-α in the skin of vitiligo patients compared to non-carriers of the disease indicates instability of cytokines in the injured regions (Pichler *et al,* 2009). Furthermore, IFN-γ has been shown to enhance recruitment of T cells to the skin by promoting intercellular adhesion molecule -1 (ICAM-1) expression (Manga & Orlow, 2012).

A possible pathogenic role has been given to changes in melanotic expression of CD117 (receptor kit) in epithelial tissue, since this coincides with the reduction in the quantity of melanocytes, such an event can be the result of the activity of cytotoxic CD8 lymphocytes present in the epidermis of patients with vitiligo (Singh et al., 2006).

Accordingly, Mosenson et al. (2012) demonstrated that the cytotoxic T cells stimulation and simultaneously downregulating Treg activity can be a consequence of overexpression of inducible heat shock protein -70 (HSP70i) to the stress response, via reduced macrophage activity and through supporting Th17-mediated autoimmunity by inflammatory cells dendritic.

Thus, evidence suggests mediated by immune cells to the pathogenesis of vitiligo responses, evidenced by the frequent observation of reactive cytotoxic T lymphocytes to melanocytes in peripheral blood of patients with vitiligo (Mantovani et al., 2003) as well as in the injured areas.

Final Considerations

Vitiligo is a condition characterized by depigmented macules resulting from the loss of melanocytes that can affect different body areas, with primarily a clinical diagnosis, except in cases that require differential diagnosis. Several treatments are available today, however, not shown cure rare, since drugs in most cases, aid in the stabilization and repigmentation.

The existences of antibodies that are present only in patients with vitiligo and anti-melanocytes activity of these antibodies justify the humoral immune response involved in the pathogenesis of vitiligo. In the studies analyzed, the TRP-1, TRP-2, tyrosinase, gp100, MCHR1 and MelanA/MART1 were the main antigens recognized by autoantibodies, these belonging to IgG and IgA.

Besides the autoantibodies, the presence of autoimmune endocrinopathies with vitiligo increases the participation of humoral immunity, whereas vitiligo precedes the onset of autoimmune diseases, it is extremely important monitoring and tracking of patients with vitiligo with respect to endocrinopathies.

The cellular immune response was also cited in the studies analyzed with patients with vitiligo, initially indicated by the presence of T cells in perilesional regions of

the macules. The cytotoxic T cells are the main involved resulting in lysis of the melanocytes, in addition, the existence of cytokines at higher levels in people with vitiligo in relation to non-carriers, mainly IL-17, strengthens the cellular immunity correlated with the disease.

Thus, environmental and physiological factors may be induces stress to the skin cells, resulting in the generation of reactive oxygen species (Manga & Orlow, 2012) and/or HSP (Mosenson et al., 2012) that cause localized melanocyte damage and death and instigates an autoimmune response that the causes melanocyte destruction in areas distant from the site of initiation (Manga & Orlow, 2012).

References

ANTELO, DP., FILGUEIRA, AL., CUNHA, JMT. Aspectos imunopatológicos do vitiligo. **Med. Cutan. Iber. Lat. Am.** 36: 125-136, 2008.a

ANTELO, DP., FILGUEIRA, AL., CUNHA, JMT. Redução dos linfócitos T-CD8$^+$ citotóxicos observada com a terapia Puva em paciente com vitiligo. **An. Bras. Dermatol**. 83: 572-574, 2008.

BARROS, JA., Machado Filho, CD'AS., MARTINS, LC., PETTINATI, J., PINHAL, MAS. Vitiligo: avaliação histológica e clínica após curetagem seqüencial. **An. Bras. Dermatol**. 82: 327-335, 2007.

BASAK, PY., ADILOGLU, AK., CEYHAN, AM., TAS, T., AKKAYA, AB. The role of helper and regulatory T cells in the pathogenesis of vitiligo. **Journal of the American Academy of Dermatology** 60: 256-260, 2009.

BASSIOUNY, D., SHAKER, O. Role of interleukin-17 in the pathogenesis of vitiligo. **Clinical and Experimental Dermatology** 36: 292-297, 2010.

BOORN, JGVD., Konijnenberg, D., Dellemijn, TAM., van der Veen, JPW., Bos, JD., Melief, CJM., Vyth-Dreese, FA., Luiten, RM. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. **Journal of Investigative Dermatology** 129: 2220-2232, 2009.

BUDEL, AR., GOMES, AMG., GONÇALVES, ACS., JORDÃO, JM., OSSOWSKI, AC., SKARE, TL. Associação entre vitiligo e doenças auto-imunes: prevalência no Serviço de Dermatologia do Hospital Universitário Evangélico de Curitiba. **Arquivos Catarinenses de Medicina**, Paraná 35: 66-70, 2006.

CASARA, C., EIDT, L., CUNHA, V. Prevalence study of dermatoses referred to the phototherapy unit at the Dermatology Service of the Clinics Hospital of Porto Alegre, RS, Brazil. **An. Bras. Dermatol**. 88: 211-215, 2013.

DANESHPAZHOOH, M., MOSTOFIZADEH G, M., BEHJATI, J., AKHYANI, M., ROBATI, RM. Anti-thyroid peroxidase antibody and vitiligo: a controlled study. **BMC Dermatology** 6: 1-5, 2006.

DWIVEDI, M., LADDHA, NC., ARORA, P., MARFATIA, YS, BEGUM, R Decreased regulatory T-cells and CD4+/CD8+ ratio correlate with disease onset and progression in patients with generalized vitiligo. Pigment Cell Melanoma 26: 586-591, 2013.

ESMAEILI, B., REZAEE, SA., LAYEGH, P., TAVAKKOL AFSHARI, J., DYE, P., GHAYOOR KARIMIANI, E, KALALINIA, F., RAFATPANAH, H. Expression of IL-17 and COX2 Gene in Peripheral Blood Leukocytes of Vitiligo Patients**. Iran J. Allergy Asthma Immunol**. 10: 81-89, 2011.

FARROKHI, S, HOJJAT-FARSANGI, M., NOOHPISHEH, MK, TAHMASBI, R., REZAEI, N. Assessment of the immune system in 55 Iranian patients with vitiligo. **J. Eur. Acad. Dermatol. Venereol.** 19: 706-711, 2005.

GEEL NV., SPEECKAERT, M., BROCHEZ, L., LAMBERT, J., SPEECKAERT, R. Clinical profile

of generalized vitiligo patients with associated autoimmune/autoinflammatory diseases. **J. Eur. Acad. Dermatol. Venereol**. 28: 741-6, 2013.

GOPAL, KV., RAMA RAO, GR., KUMAR, YH., APPA RAO, MV., VASUDEV, PS. Vitiligo: A part of a systemic autoimmune process. **Indian J. Dermatol .Venereol. Leprol.** 73: 162-165, 2007.

HARTMANN, A., BRÖCKER, EB., BECKER, JC. Hypopigmentary skin disorders: current treatment options and future directions. Drugs 64: 89-107, 2004.

HOLLA, AP., SAHNI, P., KUMAR, R., PARSAD, D., KANWAR, A., MEHTA, SD. Acral vitiligo and lesions over joints treated with non-cultured epidermal cell suspension transplantation. **Clinical and Experimental Dermatology** 38: 332-337, 2013.

KEMP, EH. Autoantibodies as Diagnostic and Predictive Markers of Vitiligo. **Autoimmunity** 37: 287-290, 2004.

MACHADO FILHO, CDAS., ALMEIDA, FA., PROTO, RS., LANDMAN, G. Vitiligo: analysis of grafting versus curettage alone, using melanocyte morphology and reverse transcriptase polymerase chain reaction for tyrosinase mRNA. **São Paulo Med. J.** 123: 187-91, 2005.

MANDELCORN-MONSON, RL., SHEAR, NH., YAU, E., SAMBHARA, S., BARBER, BH., SPANER, D., DEBENEDETTE, MA. Cytotoxic T Lymphocyte Reactivity to gp100, MelanA/MART-1,and Tyrosinase, in HLA-A2-PositiveVitiligo Patients. **The Journal of Investigative Dermatology** 121; 550-556, 2003.

MANGA, P., ORLOW, SJ. Engineering a new mouse model for vitiligo. **The Journal of Investigative Dermatology** 132: 1752-1755, 2012.

MANTOVANI, S., GARBELLI, S., PALERMO, B., CAMPANELLI, R., BRAZZELLI, V., BORRONI, G., MARTINETTI, M., BENVENUTO, F., MERLINI, G., CUNA, GR., RIVOLTINI, L., GIACHINON, C. Molecular and Functional Bases of Self-Antigen Recognition in Long-Term Persistent Melanocyte-Specific $CD8^+$ T Cells in One Vitiligo Patient. **The Journal of Investigative Dermatology** 12: 308-314, 2003.

MONTES, LF., ABULAFIA, J., WILBORN, WH., HYDE, BM., MONTES, CM. Value of histopathology in vitiligo. **Int. J. Dermatol**. 42: 57-61, 2003.

MOSENSON, JA., ZLOZA, A., KLARQUIST, J., BARFUSS, AJ., GUEVARA-PATINO, JA., LE POOLE, C. HSP70i is a critical component of the immune response leading to vitiligo. Pigment Cell Melanoma Res. 25: 88-98, 2012.

NAI, GA., MIOT, LBD., MIOT, HA., MARQUES, MEA. Imuno-histoquímica para diagnóstico precoce de vitiligo. J. Bras. Patol. Med. Lab. 44: 367-373, 2008.

NUNES, DH., ESSER, LMH. Perfil epidemiológico dos pacientes com vitiligo e sua associação com doenças da tireoide. **An. Bras. Dermatol**. 86: 241-248, 2011.

ONGENAE, K., GEEL, NV., NAEYAERT, JM. Evidence for an Autoimmune Pathogenesis of Vitiligo. **Pigment Cell Res**. 16: 90-100, 2003.

PARSAD, D., PANDHI, R., DOGRA, S., KUMAR, B. Clinical study of repigmentation patterns with different treatment modalities and their correlation with speed and stability of repig mentation in 352 vitiliginous patches. **J. Am. Acad. Dermatol.** 50: 63-67, 2004.

PICHLER, R., SFETSOS, K., BADICS, B., GUTENBRUNNER, S., BERG, J., AUBÖCK, J. Lymphocyte imbalance in vitiligo patients indicated by elevated CD4C/CD8C T-cell ratio. **Wien Med Wochenschr** 159: 337-341, 2009.

SALDANHA, KDD., MACHADO FILHO, CD'AS., PASCHOAL, FM. Ação da mometasona tópica nos halos pigmentares de microenxertia em vitiligo**. An. Bras. Dermatol**. 87: 685-690, 2012.

SINGH, ZN, TRETIAKOVA, MS., SHEA, CR., PETRONIC-ROSIC, VM Decreased CD117 expression in hypopigmented mycosis fungoides correlates with hypomelanosis: lessons learned from vitiligo. **Modern Pathology** 19: 1255-1260, 2006.

SOUZA FILHO, LGC., RIVITTI, EA., MIYAUCHI, LM., SOTTO, MN., MARIA, DA., PUEJO, SST., ALVES, VAF. Estudo comparativo entre vitiligo, nevo halo e lúpus eritematoso vitiligóide por meio de métodos imunológicos, histológicos e imuno-histoquímicos. **An. Bras. Dermatol**. 80: 143-148, 2005.

SOUZA, APFS., CARVALHO, FT., ROCHA, KB., LAGES, MN., CALVETTI, Pü., CASTOLDI, L. Associação de eventos estressores ao surgimento ou agravamento de vitiligo e psoríase. **PSICO** 36: 167-174, 2005.

SPEECKAERT, R., GEEL, NV. Distribution patterns in generalized vitiligo. **J. Eur. Acad. Dermatol. Venereol**. 28: 755-762, 2014.

TEMBHRE, MK., SHARMA, VK., SHARMA, A., CHATTOPADHYAY, P., GUPTA, S. T helper and regulatory T cell cytokine profile in active, stable and narrow band ultraviolet B treated generalized vitiligo. **Clinica Chimica Acta** 424: 27-32, 2013.

YAMAGUCHI, Y., HEARING, VJ. Melanocytes and their diseases. Cold Spring Harb **Perspect Med**. 4: 1-18, 2014.