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# Current updates about vitiligo

Vitiligo is a common skin disease and probably the most common pigmentation disease. It is well described for a long time and basically features a loss of melanocytes and/or impairment of their function. Its aetiology and pathogenesis are still not exactly understood, although progress was recently noted in this field. Treatments are aimed to achieve repigmentation, which is the patients' request. Various treatments exist, mainly topical corticosteroids or topical calcineurin inhibitors, and in case of failure of the treatment, systemic treatment with corticosteroids or methotrexate may be required, as well as physical or surgical therapies. Unfortunately none of these treatments is satisfactory, results are only partial and there is a real need for new therapeutic options improving the existing ones.

**Key words**
Vitiligo, pigmentation, aetiology, pathogenesis, treatment.

## INTRODUCTION

Vitiligo is a common chronic acquired disease of pigmentation. Its aetiology is unknown, but it is characterized by destruction of melanocytes in the skin that causes hypopigmented and asymptomatic macules with sharply demarcated margins (Fig. 1) [1].

Recent clinical and experimental studies suggest that there is a systemic destruction of melanocytes, especially in the mucous membranes, eyes, and the membranous labyrinth of the inner ear. Indeed, several authors reported an association between vitiligo, ocular manifestation, hearing loss and autoimmune diseases [3, 4]. Hearing loss is one of the most common associated symptoms with an incidence estimated in a range from 4 to 20 % of vitiligo patients [3, 4].

The term vitiligo derives from Latin and was first used by Celsus in his De Medicina [5]. However, in the nineteenth century both Brocq and Kaposi described the clinical features of vitiligo [5]. Furthermore, Kaposi showed that in the basal layer cells of the epidermis affected by vitiligo there were no pigment granules [5]. Several subsets of this condition have been reported in the literature, including localized, generalized and universal types [1].

## EPIDEMIOLOGY

By far, vitiligo is the most frequent disorder of pigmentation. India shows the highest incidence in the world (up to 8.8 %) [6]. In the U.S.A. the incidence is about 1 % [7]. However, the largest epidemiological study was conducted in 1977 in Denmark, showing an incidence of 0.38 % [8]. In addition, it is reported in the literature that about 1 % of the world's population has vitiligo [1]. Vitiligo affects both genders equally, although there is a common observation that women complain earlier and more frequently about vitiligo, possibly because in some places vitiligo is considered as a stigma or a cosmetic problem [9]. Vitiligo can develop at any age. However, in 70 %–80 % of cases it arises before the age of 30 [9]. Furthermore, an onset before the age of 12 years is common, affecting up to 37 % of patients [1].

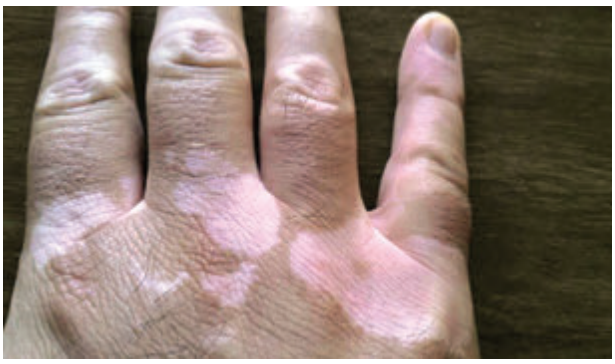

Fig. 1. **Hypopigmented macules of vitiligo with sharply demarcated margins** (2)

## GENETIC FEATURES

Vitiligo is a complex genetic disease. Fifty genes at least have already been evaluated in order to

identify a link with vitiligo. However, only a few genes present a clear association with vitiligo. On the one hand, there are non-HLA genes, including DDR1, XBP1, NLRP1, PTPN22 and COMT [10]; on the other hand, there are HLA-associated genes, including HLA-A2, HLA-DR4 and HLA- DR7 alleles [11—13]. The DDR1 gene, on the chromosome region 6p21, is involved in melanocyte adhesion to the basal layer through integrin CCN3. Indeed, recent papers highlighted that mutations in this gene generated a reduction of melanocyte adhesion in the basal membrane [14, 15]. The XBP1 gene, mapped on 22q12 locus, is implicated in the expression of MHC class II genes. Recently a paper has demonstrated an elevation in the expression of XBP1 in lesional skin of carriers of a particular XBP1 (allele C of rs2269577 polymorphism) [16]. It was shown that some variants of NLRP1, on chromosome region 17p13, were associated with the risk of generalized vitiligo and several autoimmune diseases associated with vitiligo [17]. Furthermore, the NLRP1 gene was the first to be related to American vitiligo families [17]. The PTPN22 gene, located on 1p13.3—p13.1 locus, has been recently demonstrated as an inherited risk factor to generalized vitiligo by several studies [18, 19]. The COMT gene, on 22q11.1—q11.2 locus, has been related to rising oxidative stress in vitiligo, because of its involvement in the metabolism of some catecholamines [20]. The factors mentioned above are collectively responsible of the high inherent risk of vitiligo. Indeed, it has been reported in the literature that up to 20 % of vitiligo patients show at least one first-degree relative with vitiligo [9]. Furthermore, the relative risk of developing vitiligo in first-degree siblings has been found up to tenfold higher than in general population [21].

## ETIOPATHOGENESIS

Although the aetiology of vitiligo remains unclear, several theories have been developed. However, the autoimmune hypothesis remains the leading one [2].

### Autoimmune theory

It is widely known that vitiligo can be associated with several autoimmune diseases, including autoimmune thyroid diseases, alopecia areata, halo nevi, and Addison's disease [2]. Indeed, in the literature an association has been reported between vitiligo and autoimmune diseases affecting up to 20 % of Caucasian patients [7]. Furthermore, it has been shown that autoimmune thyroid diseases, especially Hashimoto thyroiditis, are the most common vitiligo-associated disorders [7]. In addition, vitiligo could be present in all the autoimmune polyglandular syndromes (APS), especially APS-3 [22]. Finally, it was reported that Addison's disease, systemic lupus erythematosus, and inflammatory bowel diseases were all associated with vitiligo, although these were an uncommon event [7]. Although the role of anti-melanocyte antibodies in vitiligo is still not well known, high levels of circulating autoantibodies have been found in about 10 % of patients, especially against tyrosinase one and two (TRP-1 and TRP-2) [23—26]. However, their detection could be linked to the damage of keratinocytes and melanocytes. In addition, other antigenic proteins have been detected in vitiligo, including glycoprotein 153100 (gp100) and melanoma antigen recognized by T cells 1 (MART-1)154 [27]. Several papers showed $CD4^+$ and $CD8^+$ lymphocytes in the dermal-epidermal junction of areas of skin near a vitiligo lesion, highlighting the activation of cell-mediated immunity [28, 29]. A recent in vitro study identified the presence of cytotoxic T lymphocytes, that kills melanocytes in perilesional skin [30], and now it is known that HLA-A2 restricted, melanocyte-specific $CD8^+$ T lymphocytes detected in vitiligo patients are related to disease activity [31]. Furthermore, in the literature there are several reports about regulatory T cells (TREGs), which play an important role in the pathogenesis of vitiligo. More specifically, it was demonstrated that a reduction of TREGs in the peripheral blood and their dysfunctional activity raised the damage against melanocytes [32—34]. However, there are many unclear essential points about the loss of self-tolerance in the pathogenesis of vitiligo as already reported for the genesis of other autoimmune diseases [35—37].

Cytokines also have been studied in vitiligo, which is considered a Th1-related disease.

#### *Tumour Necrosis Factor-alpha (TNF-α)*

Levels of TNF-α were shown to be increased in skin biopsies of vitiligo lesions compared to normal skin [38—44]. In twenty patients with generalized vitiligo exposed to narrow-band ultraviolet B (NB-UVB) therapy thrice weekly for a total of 60 sessions, at baseline, positive lesional TNF-α expression was detected in 60 % of patients which was significantly higher as compared to perilesional skin (20 %) and negative expression in healthy control skin. Posttreatment, a statistically significant increase in TNF-α expression was detected in both lesional (90 %) and perilesional skin (70 %) as compared to baseline [44]. In the supernatant of isolated cultured PMBC of vitiligo patients after being stimulated with bacterial lipopolysaccharide (LPS), the relative percentage increase in the production of TNF-alpha was 37 %, and after intake of a daily single dose of oral aspirin (300 mg), the

decrease in the production of TNF-α was 50.6 %, which corroborates the inflammatory pattern of vitiligo [45]. Ten cases of refractory generalized vitiligo showed high tissue levels of TNF-α. Considering all 10 cases, patients with a strong TNF-α staining were characterized by a higher vitiligo disease activity score than patients with a weak staining, which suggests a probable role of TNF-α in the pathogenesis of vitiligo and that the intensity of TNF-α staining in vitiligo lesions may be worth to be further studied as a biomarker for potentially successful anti-TNF-α treatment of non-segmental vitiligo in cases refractory to conventional treatment [46]. One study explored TNF-α promoter polymorphisms and correlated them with TNF-α transcript and protein levels in vitiligo patients and controls along with its effect on disease onset and progression. The study revealed significant increase in TNF-α transcript and protein levels in vitiligo patients compared to controls. Analysis of TNF-α levels based on the gender and disease progression suggests that female patients and patients with active vitiligo had higher levels of TNF-α. Also, the TNF-α levels were high in patients with generalized vitiligo as compared to localized vitiligo. These results suggest that TNF-α promoter polymorphisms may be genetic risk factors for susceptibility and progression of the disease. The up-regulation of TNF-α transcript and protein levels in individuals with susceptible haplotypes advocates the crucial role of TNF-α in autoimmune pathogenesis of vitiligo [47]. TNF-α is thought to participate in the immunopathogenesis of vitiligo by inducing melanocyte dysfunction and death through various mechanisms. TNF-α has been demonstrated to be proapoptotic in various tissues and cell types. TNF-α is also known to be induced by and act as an inducer for nuclear factor kappa-B (NF-κB), a transcription factor involved in inflammatory and pro-survival gene promotion [48]. Death receptors belonging to the TNF receptor superfamily, such as TNF-related apoptosis- inducing ligand (TRAIL), participate in the induction of programmed cell death and play important roles in the immunopathogenesis of skin diseases [49]. TRAIL promotes apoptosis of primary human melanocytes in vitro by activation of caspases and cleavage of vital proteins [50], and melanocytes exposed to chemical stressors show increased TRAIL expression and promote dendritic cell-mediated melanocyte death [51]. Melanocyte function, including proliferation, differentiation and immunologic susceptibility to cytotoxicity can be altered by proinflammatory cytokines, including TNF-α [52]. Adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) are overexpressed in melanocytes from vitiligo lesions, and cytokines such as TNF-α can induce their expression on the surface of epidermal melanocytes [53, 54]. Moreover, TNF-α is a strong inducer of ICAM-1 in both normal and vitiliginous cultured melanocytes [55]. This pathway could influence melanocyte target recognition by T cells and mediate immunologic cytotoxic damage. TNF-α can inhibit melanogenesis by decreasing the intracellular levels of tyrosinase and tyrosinase-related protein 1, an abundant melanosomal glycoprotein involved in both melanogenesis and prevention of melanocyte death [56, 57]. There is also evidence that TNF-α-mediated inhibition of tyrosinase activity and melanogenesis is dependent on the activation of NF-κB [58]. TNF-α-treated melanocytes show marked cellular shrinking and reduced melanin production *in vitro*, as well as downregulation of MITF, a transcription factor essential in the regulation of melanocyte development, proliferation, death, and melanogenesis [59]. TNF-α leads to a dose-dependent inhibition of melanocyte proliferation, partly through increased expression of the CXC-chemokine receptor II [60]. TNF-α also leads to reduced expression of the pigment-associated antigens HMB-45 and K.1.2 in normal cultured melanocytes [61] as well as to altered immunological phenotypes. Other mechanisms of TNF-α-induced alterations in melanogenesis have been uncovered. Melanocyte-stimulating hormone receptor (MSH-R) and melanocortin-1 receptor (MC1-R) are known inducers of melanogenesis, capable of inducing the expression of melanin synthase, modulating pigmentation and melanocyte survival in normal and pathological conditions. In vitro studies of normal human melanocytes have shown that TNF-α downregulates MSHR binding activity and reduces the expression of MC1-RmRNA [62]. Using normal human melanocytes, Wang et al. [63] showed that TNF-α could stimulate the melanoma mitogens IL-8 and CXCL1, inhibit pigmentation-related signalling and melanin production, and increase the production of β-defensin 3, an antagonist for MC1-R. Melanocytes with impaired melanogenesis have altered NF-κB signalling that leads to susceptibility to TNF-α-induced apoptosis [48]. Impaired phosphatidylinositol 3-kinase/serine/threonine protein kinase activation followed by reduced NF-κB activation under increased TNF-α levels was demonstrated as a mechanism for keratinocyte apoptosis in vitiligo as well [64]. Indeed, human vitiliginous keratinocytes treated with TNF-α show increased apoptosis due to an impaired phosphatidylinositol 3-kinase/protein kinase B signalling pathway [65]. The generation of a redox imbalance and overproduction of reactive oxygen species

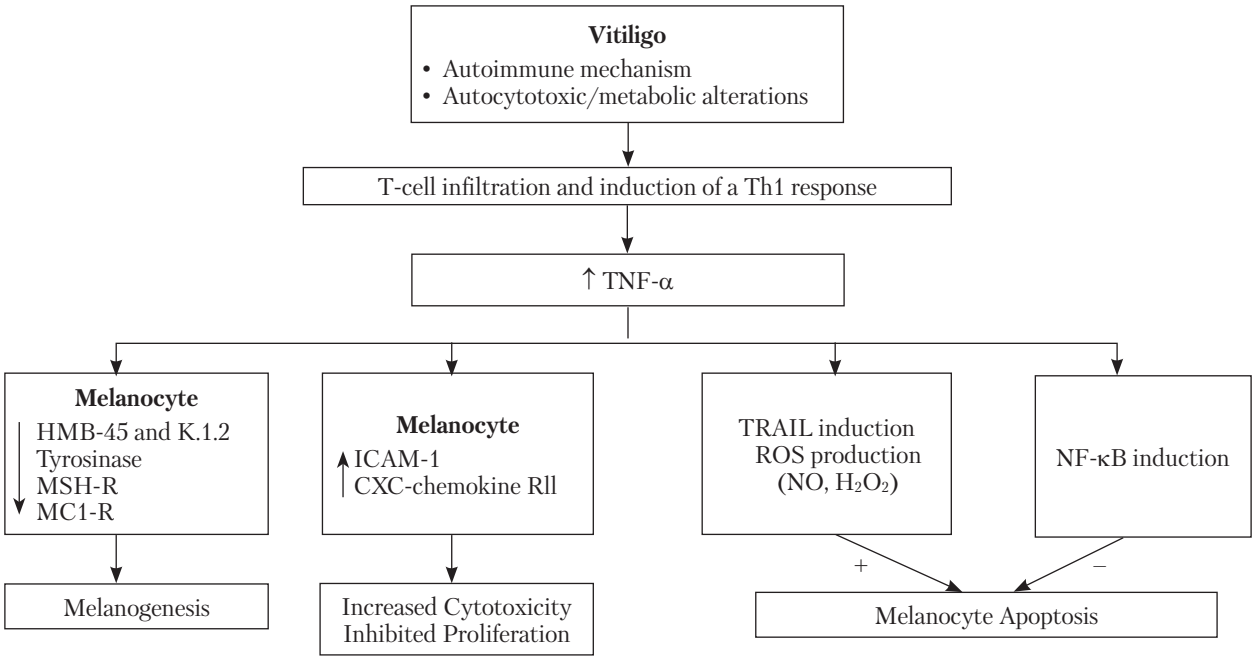


Fig. 2. **Mechanisms of TNF-α mediated alterations in melanocyte function in vitiligo** (48)

(ROS) such as nitric oxide (NO) and hydrogen peroxide ($H_2O_2$) could represent another possible mechanism of TNF-α-induced melanocytotoxicity [48]. The intracellular levels of $H_2O_2$ and other ROS increase in various cell systems in response to TNF-α stimulation [66]. In studies of in vitro human primary keratinocytes, TNF-α dose dependently and rapidly induces ROS generation, and ROS further mediate TNF-α- mediated production of inflammatory cytokines [67]. In human skin-derived cultured fibroblasts, incubation with TNF-α led to increased production of $H_2O_2$ and others ROS [68]. $H_2O_2$ can also act as a messenger in the TNF-α- dependent activation of NF-κB [69]. TNF-α is known to induce NO production in cultured melanocytes through upregulation of inducible NO synthase [70]. A similar mechanism has been observed in cultured keratinocytes, which show TNF-α-induced NO production leading to increased apoptosis [71]. A TNF-α-mediated altered redox state in the skin could then lead to membrane lipid alterations and increased mitochondrial production of ROS, resulting in melanocyte apoptosis in vitiligo [72]. The complex interplay between oxidative stress and immune mediators such as proinflammatory cytokines and T cells suggest a central role for oxidative stress — autoimmunity mediated melanocyte loss in vitiligo as well [73]. The TNF-α-associated alterations in melanocytes reviewed here (Fig. 2), coupled with evidence of increased TNF-α levels in affected skin and TNF-α gene polymorphism studies, point towards a causal role for TNF-α in the immunopathogenesis of vitiligo. Studies involving modulating TNF-α as a therapeutic strategy have been reported in the literature. A patient is described who presented with both psoriasis and vitiligo, and was treated with etanercept. After 24 weeks of therapy, the patient's psoriasis had improved markedly and the patient noted a mild improvement of vitiligo, with a reduction in macules and repigmentation in the scapular region [74]. Two cases of refractory generalized vitiligo, which showed high tissue levels of TNF-α, were commenced anti-TNF-α antibody etanercept 50 mg weekly. Etanercept achieved improvement of vitiligo in these two patients at 6-month follow-up [46]. Treated with anti-TNF agent infliximab, with the improvement of ankylosing spondylitis, a patient's vitiligo lesions also faded out [75]. Recently, Webb et al. [76] have reviewed the literature pertaining to the use of anti-TNF-α mediators such as infliximab, etanercept and adalimumab as therapeutic tools for vitiligo. Their findings revealed that blocking the action of TNF-α effectively stopped the progression of vitiligo and initiated repigmentation in almost all patients with active disease, presumably at least in part due to the stemming of cytotoxic T-cell-mediated destruction of melanocytes. Importantly, the researchers noted that the arrest of melanocyte loss was as valid in assessing the success of treatment as observing actual repigmentation, concluding that future clinical trials will need to effectively evaluate both parameters. Interestingly,

the literature reported a small proportion of patients without vitiligo who were receiving treatment with TNF-α antagonists adalimumab and infliximab for other autoimmune diseases and who developed depigmentation. The authors of the review suggest that this phenomenon results from a decrease in the production and activation of regulatory T cells (Tregs), which are normally stimulated by TNF-α and act to supress cytotoxic T-cell activity. If Treg cell numbers are reduced in the skin, then T lymphocytes cytotoxic to melanocytes may exert their effects leading to pigment cell loss. Overall, inhibitors of TNF-α were found to be beneficial for patients with progressing vitiligo.

*Interferon-γ (IFN -γ)*

Increased expression of the cytokine interferon (IFN)-γ plays a pivotal role in vitiligo-induced depigmentation [77]. In a study, a large number of skin infiltrating IFN-$\gamma^+$ cells and $CD8^+$ T cells were detected in progressive vitiligo [77]. Among the peripheral blood mononuclear cells (PBMCs) of vitiligo patients, $CD8^+$ cytotoxic T lymphocytes (CTLs) that express IFN-γ exhibited significant expansion, which suggests that activated CTLs are the main source of increased IFN-γ in progressive vitiligo [77]. In the same study, it was demonstrated that IFN-γ inhibits melanogenesis in primary cultured human melanocytes by altering melanogenic enzyme mRNA expression and, more importantly, that IFN-γ directly induces melanocyte apoptosis. Son et al. [78] had previously demonstrated that IFN-γ inhibits basal and α-MSH-induced melanogenesis in B16 melanoma cells and normal human melanocytes. MITF mRNA and protein expressions were significantly inhibited in response to IFN-γ. These findings suggest that IFN-γ inhibits both basal and α-MSH-induced melanogenesis by inhibiting MITF expression and that IFN-γ plays a role in controlling inflammation- or UV-induced pigmentary changes [78]. In a recent study [79], treatment with IL-18 resulted in a dose dependent increase of melanogenesis, while IFN-γ made an opposite effect. This influence of IL-18 and IFN-γ was mediated by regulations of microphthalmia-associated transcription factor (MITF) and its downstream enzymatic cascade expressions. Furthermore, IFN-γ inhibited basal and IL-18-induced melanogenesis. IFN-γ could also inhibit melanogenesis by decreasing melanocyte dendrite formation. In addition, IFN-γ inhibited the expressions of Rab Pases to suppress the mature and transport of melanosomes. It was also reported that IFN-γ can induce senescence in melanocytes and consequently enhance their immuno-competency, leading to a vitiligo-prone milieu [80].

*Interleukins (IL)*

Interleukin-1α (IL-1α) is remembered as one of the cytokines of inflammation, and is also known as a B-cell activating factor. It produces similar biological effects with TNF α and is produced in most inflammatory and immunological diseases. Among 24 patients with symmetrical generalized, acrofacial and focal vitiligo, as well progressive as stable, the expression of IL-1α was significantly higher in lesional skin than in non-lesional skin in these patients [40]. Swope et al. investigated the role of epidermal cytokines in pigmentation and found that IL-1α, TNFα, and IL-6 elicited a dose-dependent decrease in the activity of the enzyme tyrosinase of cultured normal human melanocytes and also inhibited melanocyte proliferation [81]. As regards interleukin-6 (IL-6), in 15 patients with active, non-segmental vitiligo, biopsies were obtained from lesional, perilesional and non-lesional skin; normal skin from five healthy donors was also tested [41]. A significantly higher expression of IL-6 was detected in lesional skin, compared with perilesional, non-lesional and healthy skin. A significant increase in spontaneous production of IL-6, but also IL-8 was found in serum of patients suffering from active vitiligo compared with healthy controls [82]. Twenty patients with generalized vitiligo were treated with tacrolimus 0.1 % ointment applied twice daily. At baseline, compared with healthy controls, vitiligo patients demonstrated a statistically significant increase in the expression of IL-10 in involved and uninvolved skin [83] but posttreatment there was no significant change. IL-17 also has been found at higher levels in the blood and tissues of patients. Its activity influences the production of TNF-α, which is also elevated in vitiligo [84]. In addition, it has been shown that the persistence of vitiligo is related to IL-17 levels [84].

Among the melanogenic mediators, stem cell factor (SCF) was significantly reduced in lesional as compared to perilesional epidermis in vitiligo patients [38, 41]. There are divergent results about basic fibroblast growth factor (bFGF). In two studies [39, 41] the level of bFGF mRNA was significantly lower in lesional skin of vitiligo than in the control skin once in another one [40] no statistically significant difference between the study and the control group was observed in terms of b-FGF levels.

## Adhesion defect theory

In 2003 Gauthier et al. postulated that non-segmental vitiligo (NSV) could be caused by a chronic detachment of melanocytes provoked by trauma, mainly a mechanical rubbing of healthy skin [85]. This concept is now known as «melanocytorrhagy

theory». Furthermore, Gauthier et al. hypothesized that an autoimmune activation could be provoked by dendritic cells or memory T cells detecting autoantigens during melanocytorrhagy through the epidermis basal layer [86]. As a result of the above findings, some adhesion proteins have been studied to explain the loss of melanocytes. Le Poole et al. [87] highlighted that tenascin, an extracellular matrix molecule involved in adhesion, was increased in vitiligo patients, thus reducing melanocyte adhesion.

### Biochemical theory

Oxidative stress is considered to be one of the possible pathogenic events in melanocyte loss [88, 89]. Defective recycling of tetrahydrobiopterin in whole epidermis of patients with vitiligo is related to the intracellular production of $H_2O_2$ [90, 91]. In addition, an increased intracellular production of ROS due to mitochondrial impairment [92] and a compromised antioxidant status [89, 93, 94] supports the concept of a possible systemic oxidative stress in vitiligo. This accumulated oxidative stress causes DNA damage, lipid and protein peroxidation. Many proteins are altered and show partial or complete loss of functionality due to $H_2O_2$-mediated oxidation. $H_2O_2$ can also function as an inhibitor of tyrosinase, or in the presence of $H_2O_2$, DOPA (dihydroxyphenylalanine) substrate can generate a secondary complex that can bind and inhibit tyrosinase [95]. Elevated extracellular calcium levels and inhibition of thioredoxin reductase also contribute to the generation of oxidative stress in the vitiligo epidermis [96, 97]. Several sources have been documented for the unusual production/accumulation of epidermal $H_2O_2$. Studies also showed systemic oxidative stress in patients with vitiligo due to an imbalance in enzymatic and non-enzymatic antioxidant systems [98, 99] and significant decrease in acetylcholine esterase (AChE) activity [100], which could be due to $H_2O_2$-mediated oxidation of AchE [101], thus emphasizing the role of oxidative stress in precipitation of vitiligo. Moreover, this study suggests oxidative stress as the initial triggering factor in precipitating vitiligo. Patients with early onset (< 3 months) of vitiligo showed significant decrease in the levels of antimelanocyte antibodies compared to patients with long duration (> 3 months), and moreover, erythrocyte lipid peroxidation levels were significantly increased in patients with early-onset vitiligo compared to patients with long-standing vitiligo [101]. The intracellular levels of $H_2O_2$ and other ROS also increase in response to cytokines such as TNF-α and TGF-β1 (transforming growth factor b1), which are potent inhibitors of melanogenesis [100, 101, 110]. High ROS also increase the levels of cytokines, including IL-2 (interleukin-2), which upregulate the expression of anti- apoptotic protein, Bcl-2 (B-cell lymphoma-2), thereby making T cells resistant to apoptosis [102]. In a recent work [103] it was found that miR-25 was increased in both serum and lesion samples from vitiligo patients, and its serum level was correlated with the activity of vitiligo. Moreover, restoration of miR-25 promoted the $H_2O_2$-induced melanocyte destruction and led to the dysfunction of melanocytes. Further experiments proved that MITF, a master regulator in melanocyte survival and function, accounted for the miR-25-caused damaging impact on melanocytes. Notably, other than the direct role on melanocytes, it was observed that miR-25 inhibited the production and secretion of SCF and bFGF from keratinocytes, thus impairing their paracrine protective effect on the survival of melanocytes under oxidative stress. At last, it could be verified that oxidative stress could induce the overexpression of miR-25 in both melanocytes and keratinocytes possibly by demethylating the promoter region of miR-25. Taken together, this study demonstrates that oxidative stress-induced overexpression of miR-25 in vitiligo has a crucial role in promoting the degeneration of melanocytes by not only suppressing MITF in melanocytes but also impairing the paracrine protective effect of keratinocytes [103].

## CLASSIFICATION AND CLINICAL FEATURES

### Classification

Vitiligo is divided clinically into two main forms, segmental vitiligo (SV) and non-segmental vitiligo (NSV) respectively. The latter also includes three major subsets, namely generalized vitiligo, acrofacial vitiligo, and universal vitiligo [1]. Recently, mixed vitiligo (MV) has been described as an initial SV, which later (usually several months) spreads bilateral NSV patches [104]. However, because the progress of vitiligo is unpredictable, it is not uncommon for NSV to evolve over time, modifying its extension and distribution [2]. Despite this clear classification, two unclassified forms are reported in the literature, namely focal vitiligo and mucosal vitiligo [105]. Focal vitiligo is characterized by few, small, and isolated white macules without a segmental distribution that fails to progress to NSV after a couple of years from onset. Mucosal vitiligo is identified by the presence of only oral or genital mucosa involvement. However, when vitiligo affects a mucosa in the context of an NSV, it is considered a true NSV. The different subtypes of vitiligo are summed up in Table 1.

Table 1. **Classification of vitiligo** (2)

| NOMENCLATURE | SUBSET | |
|---|---|---|
| Non-segmental vitiligo | Acrofacial | Usually limited to face, head, hands, and feet |
| | Generalized | Symmetrical macules, mainly hands, fingers, face, and trauma-exposed areas |
| | Mucosal (at least two sites involved) | Involvement of the oral and/or genital mucosae with other sites of skin involvement |
| | Universal | Depigmentation affects 80—90 % of body surface |
| Segmental vitiligo | Unisegmental | One or more depigmented macules distributed on one side of the body |
| | Bisegmental | Two segmental lesions distributed either unilaterally or bilaterally |
| | Plurisegmental | Multiple segmental lesions distributed either unilaterally or bi-laterally |
| Mixed vitiligo | Occurrence of SV and NSV | SV followed by NSV with a delay of at least 6 months. At least 20 % of a dermatomal segment affected by SV |
| Unclassified vitiligo | Focal vitiligo | Isolated macules that do not have a segmental distribution. No evolution into NSV after at least 2 years |
| | Mucosal vitiligo (only one site involved) | Exclusive involvement of the oral or genital mucosae |

### Skin features

The most typical skin lesion is an asymptomatic whitish macule or patch, with regular borders and sharp margins, surrounded by normal or hyperpigmented skin. Rarely, patches have inflamed borders with pruritus [1]. The onset of the lesions is insidious and the development of the disease is unpredictable. Hairy areas also can be affected. In this case, the hair follicles are typically white. An early age of onset is associated with familial occurrence and often determines a more severe disease [7]. In NSV, lesions usually arise on areas exposed to a chronic trauma, especially the hands or the arms. Indeed, it has been observed that vitiligo lesions may be related to repeated rubbing during daily activities, like personal care or occupation activities. Macules can also appear in areas submitted to pressure from tight- fitting clothes.

### Ocular features

The choroid and retinal pigment epithelium (RPE) are similar to the skin in that they display the presence of well differentiated melanocytes, with a common origin: the neural crest. In the eye, these melanocytes contribute to retinoid production and protection against UV rays [2]. In the literature few papers have dealt with ocular findings in vitiligo. However, the association between ocular diseases and vitiligo is well known, because vitiligo is a feature of both Vogt–Koyanagi–Harada syndrome [106] and of sympathetic ophthalmia [107]. Also, the association between vitiligo and uveitis is well known [108]. Regarding the wide spectrum of ocular diseases that can affect vitiligo patients, Biswas et al. [109] demonstrated several ocular features in a sample of 100 vitiligo patients, including hypopigmented spots on the iris (23 %), pigmentation on the anterior chamber (18 %), chorioretinal degeneration (11 %), RPE hypopigmentation (9 %) and uveitis (5 %). In addition, two studies conducted on large series reported that more than 40 % of vitiligo patients had noticeable areas of hypopigmentation affecting the choroid or retinal pigment epithelium [110, 111].

### Audiological abnormalities

The membranous labyrinth of the inner ear contains melanocytes and pigmented cells are also present in the scala vestibuli. Despite the fact that the specific functions of otic melanocytes are still unclear, clinical and experimental studies suggest that melanin has semi-conductive properties, responding to acoustic and electrical stimulations. Furthermore, these cells have the ability to convert energy states into molecular rotation and vibration as well as reversing the process [2]. Several authors studied the association between vitiligo and hearing loss, which was detected in a range from 4 to 20 % of vitiligo patients [4, 112, 113].

## CURRENT THERAPY

The aim of the treatment is to obtain skin repigmentation. It is a common observation that some areas, especially those damaged by a chronic physical trauma (e.g. the hands), are less responsive to the therapy. However, spontaneous repigmen-

tation occurs in between 1 and 25 % of patients [114].

### Topical steroids

Topical corticosteroids (TCs) are still the mainstay of treatment for localized forms of vitiligo [115]. Although they have several widely known side effects, such as atrophy or telangiectasia, TCs are considered as first-line therapy because of their wide availability, low cost and efficacy [116]. Several papers report that high-potency TCs are more effective on small lesions, but some authors prefer low-potency TCs on flexural areas and on the face because of their thinness [117]. Vasistha et al. [118] proposed the use of intralesional steroids to treat small lesional areas, but it was reported that upper mid-strength TCs had higher efficacy [119]. Furthermore, in the same paper the authors emphasized that upper mid-strength TCs had a higher efficacy and produced less atrophy compared to mid-strength TCs [163]. Regarding the high power TSs, it has been reported that they should be used for no longer than 2—4 months [120].

### Calcineurin inhibitors

This class of drugs includes two topical immunosuppressants, namely tacrolimus and pimecrolimus. Compared to TCs, topical calcineurin inhibitors (TCI) do not provoke skin atrophy [164]. Although in 2005 the FDA issued a public health advisory regarding a possible association between TCIs and malignancy (e.g. squamous cell carcinoma, basal cell carcinoma, T-cell lymphoma), no definite relationship between TCIs and malignant tumours was reported [121]. On the one hand, a double blind randomized controlled study highlighted that tacrolimus 0.1 % ointment was almost as efficacious as clobetasol propionate 0.05 % ointment [122]. Furthermore, Choi et al. [123] found that tacrolimus was equal to upper mid-strength TCs in promoting repigmentation. In addition, recent reports have shown that a twice-weekly application of 0.1 % tacrolimus ointment prevents the depigmentation of vitiligo patches that have been previously treated with success [124]. On the other hand, mixed results were reported regarding pimecrolimus. A double blind randomized controlled study has demonstrated that pimecrolimus is ineffective on body lesions [125]. Furthermore, Eryilmaz et al. [126] demonstrated that clobetasol propionate 0.05 % was superior to pimecrolimus 1 % cream for inducing repigmentation. However, in an open study Lubaki et al. [127] reported that pimecrolimus works statistically better for the face than for the upper limbs. Additionally, Coskun et al. [128] reported that pimecrolimus 1 % cream was just as efficacious as clobetasol propionate 0.05 % ointment. Another therapeutic approach is to use excimer laser therapy and TCIs in combination. Kawalek et al. [129], in their double- blind study, reported that tacrolimus 0.1 % ointment plus excimer laser was more effective than placebo plus excimer laser. Furthermore, Nistico et al. [130] demonstrated that the combination treatment of 0.1 % tacrolimus ointment plus 308 nm excimer laser was effective and safe in vitiligo patients. In addition, in a comparative, randomized, single-blinded study a better outcome was found in groups treated with 1 % topical pimecrolimus associated with excimer laser (308 nm) than laser alone [131]. Regarding topical tacrolimus, some papers in the literature have dealt with an association between tacrolimus ointment and UV sources. In a double-blind study, it was reported that tacrolimus 0.1 % ointment plus narrow-band UVB (NB-UVB) reduced the size of vitiligo lesion more efficaciously than NB-UVB alone [132]. Majid [133] also reported that the combination of tacrolimus 0.1 % ointment and NB-UVB resulted in better repigmentation rates and decreased NB-UVB exposure compared to the NB-UVB alone.

### Systemic therapy

Although some different approaches have been attempted in cases of disseminated vitiligo lesions, steroids still remain the principle therapy. However, a recent study, conducted on six patients, reported that oral methotrexate was a safe and effective therapy for vitiligo [134]. A non-comparative study reported that the administration of i. v. prednisolone (0.3 mg/kg/day) guaranteed the control of disease progression and repigmentation [135]. Radakovic-Fijan et al. [136] also reported that weekly pulses of 10 mg dexamethasone therapy reduced the progression of vitiligo, but failed to induce repigmentation. In a prospective, randomized, clinical trial, Seiter et al. [137] reported that i. v. methyl-prednisolone (8 mg/kg bodyweight) on 3 consecutive days was effective to treat generalized progressive vitiligo.

### Physical therapy

There are three main types of physical therapy for vitiligo, namely narrow band UVB, phototherapy with UVA and psoralens (PUVA therapy) and monochromatic excimer light (MEL). NB-UVB (311 nm) is now considered one of the most effective and safest types of therapy for vitiligo [115—138]. Indeed, many papers have shown that it is safer and more effective than psoralen UVA (PUVA) therapy [139—141]. It has been widely reported that NB-UVB reached the same or better

results in repigmentation compared to PUVA [142, 143]. In addition, NB-UVB was not found to increase the risk of melanoma and non-melanoma skin cancers [144], while PUVA slightly increases the risk of both melanoma and non-melanoma skin cancers [145]. NB-UVB alone reaches repigmentation rates between 41.6 and 100 % [146, 147]. On the other hand, PUVA therapy requires the use of UVA (320—400 nm) and of a photosensitizing drug, commonly 8 methoxypsoralen per os. Because of its side effects, including a higher risk of squamous cell carcinoma of the skin, cutaneous phototoxicities, and nausea, NB-UVB is now preferred to PUVA therapy [139]. However, some authors reported good results with PUVA therapy [148, 149]. MEL is the best known laser therapy for vitiligo. In particular, the xenon chloride MEL has a wavelength of 308 nm. Several papers reported high success rates of successful results when it is used alone, with response rated as high as 95 % [150—152]. It was also highlighted that MEL produced better outcomes than NBUVB [153].

### Surgical therapy

Surgical therapy could be useful in patients in whom medical therapy has failed: several surgical techniques are usually employed. The blister graft technique involves the creation of a subepidermal bulla from the donor site. The roof of the bulla is then collocated into the recipient area, prepared to allow the uptake of the graft using different techniques to obtain an abraded surface [154, 155]. Several procedures to obtain the bulla have been reported in the literature [155, 156]. It was reported that this process determined a complete repigmentation in up to 90 % of patients [157]. However, the Koebner phenomenon could be a cause of failure of this procedure [158]. The split-thickness skin graft could be used to induce repigmentation in large areas. A dermatome is needed to obtain a uniform skin graft. According to Agarwal et al. [158], it is possible to obtain repigmentation rates up to 100 %. Two limiting aspects could be the incompatibility of colours in the receiving area and the need for an expert surgeon, because the dermatome is not simple to use [158]. Punch grafting is the simplest and cheapest surgical procedure. However, it seems to be useful only when small areas are involved [159]. The recipient site is drilled by multiple punches, allowing the uptake of cylindrical fragments from the donor area. Malakar et al. [160] reported 90 to 100 % repigmentation rates in 74.5 % of the patients treated. In addition, NB-UVB could be combined with punch grafting to obtain even better results [161]. The autologous melanocyte suspension transplant (AMST) is a complex technique, which is composed of three steps: obtaining skin from the donor area, preparing a suspension of keratinocytes and melanocytes, and transplanting to the recipient site. Van Geel et al. [162] reported a repigmentation rate of at least 70 in 77 % of patients after 12 months. It has been reported that lesions in particular areas, including fingers, legs, and ankles displayed the best results, whereas facial lesions had a poor response [163]. However, this procedure is very expensive and requires a tissue culture laboratory.

## CONCLUSION

Vitiligo is a common skin disease, and features the most common pigmentation disorder. Vitiligo is not contagious, not painful and does not induce physical disturbance. The disease is «only» of cosmetic concern but deeply affects the QoL, self-esteem and psychosocial life of patients. For this reason a better knowledge of its pathogenesis and consequent proposal of new treatments is important in order to improve the offer of potential treatments to vitiligo patients, as there is currently no satisfactory way of dealing with the disease.

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# Вітиліго: нові дані

Вітиліго — поширене захворювання шкіри і, ймовірно, найпоширеніше порушення пігментації. Воно добре описано і характеризується втратою меланоцитів і/або порушенням їхньої функції. Етіологія і патогенез вітиліго досі не до кінця з'ясовані, хоча недавно відбувся прогрес у цій сфері. Лікування спрямоване на досягнення репігментації, яка є бажаним результатом у пацієнтів.

Існують різні методи лікування. Переважно призначають місцеві кортикостероїди або інгібітори кальцинейрину, а якщо не досягають бажаних наслідків, можуть вдаватися до системного лікування кортикостероїдами або метотрексатом, а також фізичної чи хірургічної терапії. На жаль, жоден з цих методів лікування не можна вважати повністю результативним, оскільки досягають лише часткового поліпшення. Отже, існує нагальна потреба в розробці нових терапевтичних методів.

**Ключові слова:** вітиліго, пігментація, етіологія, патогенез, лікування.

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# Витилиго: новые данные

Витилиго — распространенное заболевание кожи и, вероятно, наиболее распространенное нарушение пигментации. Оно хорошо описано и характеризуется потерей меланоцитов и/или нарушением их функции. Этиология и патогенез витилиго до сих пор до конца не изучены, хотя недавно был отмечен прогресс в этой области. Лечение направлено на достижение репигментации, которая является желаемым результатом у пациентов.

Существуют различные методы лечения. В основном применяют местные кортикостероиды или ингибиторы кальцинейрина, а в случае отсутствия результатов может потребоваться системное лечение кортикостероидами или метотрексатом, а также физическая или хирургическая терапия. К сожалению, ни один из этих методов нельзя считать полностью результативным, так как обеспечивается лишь частичное улучшение. Поэтому существует настоятельная потребность в новых терапевтических методах.

**Ключевые слова:** витилиго, пигментация, этиология, патогенез, лечение.

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