INTRODUCTION

Vitiligo is a chronic acquired and progressive disease, characterized by the appearance of achromic macules that are isolated or found in multiple body segments, due to the absence of melanin ***(Tarlé et al., 2014)*** with prevalence of 0.5-2% of the general population ***(Krüger and Schallreuter, 2012).***

The condition does not produce a physical handicap, and it is asymptomatic but it can cause significant psychosocial distress in patients, ultimately affecting their self-esteem, their personal relationships, and even their employment ***(Silverberg and Silverberg, 2014).***

The exact etiology of vitiligo have been proposed of many competing theories, the most prominent theories include autoimmune, oxidative, neural, genetic, viral and psychological theories ***(Ezzedine et al., 2016).***

Vitiligo has been classified according to the clinical ground into two major forms, namely segmental vitiligo (SV) and non-segmental vitiligo (NSV), the latter includes several variants (generalized, acro facial and universal ***(Taieb and Picardo, 2007).***

Several treatment modalities had been used for the treatment of vitiligo such as corticosteroids, immune-modulators, analogues of vitamin D3, diverse types of phototherapy [ultraviolet B (UVB), psoralen plus UVA

(PUVA), narrow-band UVB (NB-UVB) and targeted phototherapy], excimer laser and surgery/transplantation ***(Forschner et al., 2007)***, but the optimal treatment has not yet been identified ***(Abd El-Samad and Shaaban, 2012).***

Narrow-band ultraviolet B (NB-UVB) is considered the most effective and safe initial treatment for moderate-to-severe vitiligo but phototoxicity and possible carcinogenicity are the reported side effects ***(El-Zawahry et al., 2012)***.

The predominant type of re-pigmentation after NB-UVB is perifollicular. Therefore, it is at least theoretically justified to believe that it has some relation to the melanocytes reserve in the outer root sheath ***(Parsad et al., 2010).***

Psoralen is a photosensitive compound that belongs to the coumarin family, is isolated from *Fructus psoraleae* to 3 compound (8-methoxypsoralen, 5-methoxypsoralen, and 5-isoamyleneoxypsoralen) ***(Hönigsmann, 2013)***.

Psoralen was used to treat vitiligo through exposure to sunlight or ultraviolet radiation ***(Sapam et al., 2012)***. Treatment with psoralen may increase tyrosinase activity and promote melanin synthesis in normal melanocytes adjacent to the damaged cells ***(Ozkan et al., 2012)***.

Aim of the Work

The aim of this work was to evaluate the efficacy and safety of topical psoralen-narrow band ultraviolet B for the treatment of non-segmental vitiligo in comparison to narrow band ultraviolet B alone.

Chapter 1

VITILIGO

Vitiligo is an acquired chronic depigmenting disorder of the skin, characterized by the development of white macules resulting from a loss of epidermal melanocytes ***(Picardo et al., 2018)***. It causes no fatality but significant psychosocial consequences ***(Wu et al., 2013).***

Vitiligo is not only a disease of melanocytes of the skin as human melanocytes are derived from the neural crest thus are located on various parts of the body. The involvement of skin melanocytes is the most visible one, but a systemic involvement of melanocytes can be observed ***(Lotti and D`erme, 2014)***.

Epidemiology:

Vitiligo is an acquired idiopathic disorder with the worldwide prevalence that ranges between 0.5 and 2% ***(Krüger and Schallreuter, 2012).*** It probably has a higher incidence in dark-skinned individuals ***(Gauthier et al., 2013).***

The course of the disease is unpredictable, it is often progressive with stable phases in between during which there is no more depigmentation. Progressive disease with extending, enlarging macules or with appearance of new depigmented lesions is classified as active vitiligo ***(Gawkrodger et al., 2010).***

It affects all people with no predilection in gender, race, or skin type ***(Alikhan et al., 2011).*** The recorded predominance of women may be due to their greater willingness to express concern about cosmetically relevant issues. Half of all patients develop the disease before 20 years of age ***(Kyriakis et al., 2009).***

Clinical picture:

Vitiligo is a disease characterized by the appearance of well circumscribed depigmented patches. The typical vitiligo macule is chalky or milky–white colour, is round to oval in shape, has slightly brushed to fairly distinct, often scalloped margins, measures from several millimetres to many centimetres in diameter, and usually lacks other epidermal changes ***(Taieb and Picardo, 2007).***

Morphological variants include: trichrome vitiligo, where three shades in concentric zones are noted; normal, intermediate depigmentation and full depigmentation. Inflammatory vitiligo, where there is an erythematous, raised border of the lesion, with associated itching. Ordinary vitiligo can also present with pruritus. Sometimes a hyperpigmented rim can be seen at the outer margin of a vitiligo lesion, especially after sun exposure. The loss of hair pigment in affected areas is considered a late sign of vitiligo, with some prognostic significance. Therefore, it appears that epidermal melanocytes are lost before those in the hair bulb ***(Glassman, 2011).***

Vitiligo Lesions can begin anywhere in the skin. However, more frequently they initially appear around the mouth, the eyes, axilla, umbilicus, nipples, on the fingers, wrists and over the elbows and knees; areas with the most physical microtrauma ***(Boissy and Nordlund, 2011).***

In non segmental vitiligo (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. These kinds of stimuli are responsible for koebnerization ***(Ezzedine et al., 2012)***.

Lesions enlarge centrifugally over time but the rate may be slow or rapid. In very lightly pigmented people, the lesions are not very apparent but they are easily distinguishable with Wood's lamp examination or after tanning of uninvolved skin ***(Ortonne and Passeron, 2012)*** **(figure 1).**

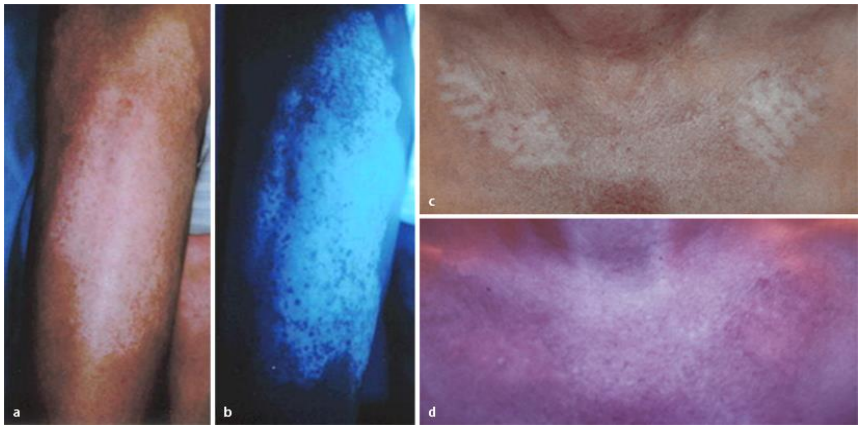

Figure (1): a. Vitiligo (clinical picture) **b.** Under Wood's lamp show bluish white fluorescence **c.** Laser induce leukoderma (clinical picture) **d.** No fluorescence is detectable under Wood's lamp ***(Schallreuter and Salem, 2010)***.

The ocular manifestation also can be seen in vitiligo patient. 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 ultraviolet (UV) rays. 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 Vogt-Koyanagi-Harada syndrome ***(Greco et al., 2013)***.

Vitiligo is also associated with audiological abnormalities. Several studies revealed the association between vitiligo and hearing loss, which was detected in 4% to 20% of vitiligo patients ***(Akay et al., 2010; Fleissig et al., 2013)***. Melanocytes are present in the membranous labyrinth of the inner ear and are

also present in the scala vestibuli. Despite the fact that specific functions of otic melanocytes are still unclear, clinical and experimental studies suggested 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. In addition, the melanin is reported to have a protective role against environmental damage ***(Mahdi et al., 2012)***.

- ***Precipitating Factors:***

i. Psychological:

- Psychological trauma such as crisis, illness, loss of job, death of a close family member, an accident, or a severe systemic disease may increase individual's susceptibility to vitiligo ***(Guerra et al., 2010)***. Life quality also influenced by vitiligo leading to depression in the affected individual ***(Sangma et al., 2015).*** It was confirmed that in > 50% of the vitiligo patients, emotional stress is the triggering factor ***(Vrijman et al., 2013).***

ii. Physical injury:

In some patients the onset of vitiligo follows a physical injury such as a cut or abrasion, or sun exposure; this development of focal vitiligo congruent with a site of injury is referred to as the isomorphic köebner phenomenon ***(Ortonne et al., 2003; Batalla and Feal, 2010).*** It is observed in up to 40%

of patients mostly those with non-segmental vitiligo***; Dhar et al., 2014)*** **(figure 2)**.

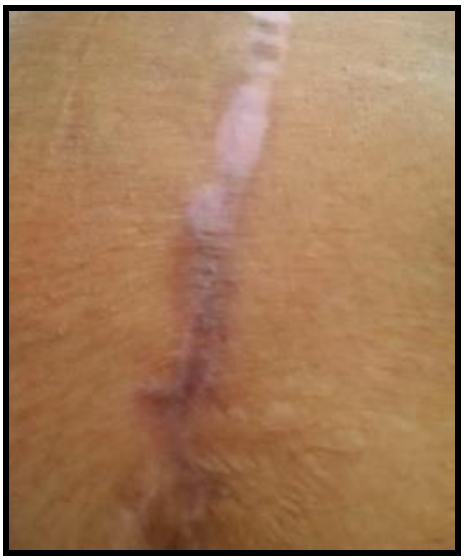

Figure (2): Koebner phenomenon: depigmented area in a scar after abdominal surgery in vitiligo patient ***(Schild and Meurer, 2016).***

iii. Nutrition:

There is a potential link between nutrition and pathophysiology of vitiligo due to the important contribution of reactive oxygen species (ROS), estrogen, tannin, and phenol-containing chemicals which can compete with tyrosine to produce reactive quinones ***(Namazi and Chee Leok, 2009).***

Mango, cashew, pistaschio, oak, cassava, areca nut, red chillies, cherry, raspberry, cranberry, blackberry and tea contain naturally occurring plant phenol and polyphenolic compounds (tannins), which may aggravate vitiligo ***(Birol et al., 2006).***

iv. Drugs:

Vitiligo can be induced by anticonvulsants (carbamazepine, valproic acid), antimalarial drugs (chloroquine), biological drugs (infliximab) and other drugs (clofazimine, dopamine) in some reported cases. Pathomechanisms of reported cases can be classified into 3 groups: **a.** drug-induced activation of cytotoxic T cells directed against melanocyte antigens (melanoma antigen recognized by Tcells1 (MART-1)/ Melanoma antigen (MelanA), glycoprotein (gp) 100, Tyrosine related protein 1(TRP-1), Tyrosinase related protein 2 (TRP-2)), **b.** drug-induced damage to sympathetic nerves that are connected by chemical synapses to melanocytes, which indirectly leads to their functional disturbances, **c.** direct, cytotoxic effects of drugs on melanocytes (apoptosis) ***(Curzytek et al., 2007)***. Other medications that can cause disease provocation are β-blockers, statins and tetracycline and cosmetic ingredients such as topical coenzyme Q10 (ubiquinone) ***(Schallreuter and Salem, 2010).***

iv. Pregnancy:

The effect of pregnancy on vitiligo is variable, it may aggravate, improve, or cause no effect. However the disease usually worsens after delivery ***(Patel et al., 2003).***

Classification:

The classification of vitiligo has been revised. Originally the classification had a number of categories i.e. generalized,

focal, acrofacial, total, inflammatory, contact/occupational and unilateral (segmental). Some of these i.e. acrofacial, generalized and total probably are phases of the same disorder. Therefore it was recommended that vitiligo can be classified into two forms: vitiligo vulgaris/ non-segmental (NSV) and segmental vitiligo (SV) ***(Boissy and Nordlund, 2011).***

Mixed vitiligo (MV) has been defined as the combination of initial SV followed by the occurrence of bilateral NSV patches several months or, more rarely, years later ***(Ezzedine et al., 2011).*** The Vitiligo Global Issues Consensus Conference (VGICC) added another nomenclature/classification for vitiligo in 2011 **(table 1)** ***(Ezzedine et al., 2012).***

Table (1): Bordeaux VGICC classification and consensus nomenclature ***(Ezzedine et al., 2012).***

Type of vitiligo	Subtypes
Non – segmental vitiligo	Acro – facial
	Mucosal (more than one site)
	Generalized
	Universal
	Mixed
	Rare subtypes
Segmental vitiligo	Uni -, bi - or plurisegmental
Undetermined / unclassified vitiligo	Focal
	Mucosal (only one site)

A- ***Vitiligo/Non Segmental vitiligo***

The term 'vitiligo' (V) is the recommended umbrella term for all non-segmental forms of vitiligo. As a transition, vitiligo/NSV can be used. it is the most common form of the disease (accounting for 85% to 90% of cases). The lesions of NSV are usually bilateral, frequently symmetrical **(figure 3)** and generally progressive. This disease may begin in childhood but a later onset is more common ***(Guerra et al., 2010)***.

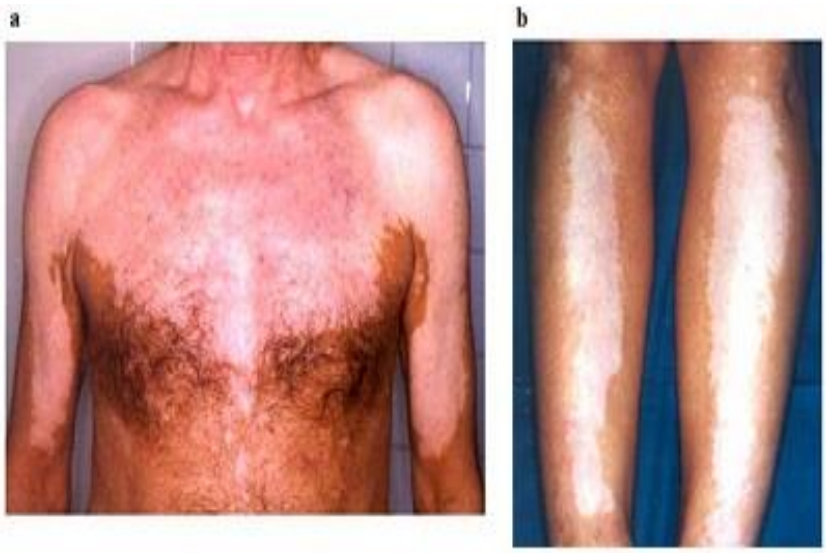

Figure (3): Non segmental vitiligo (NSV) ***(Guerra et al., 2010).***

1) Generalized vitiligo (GV):

Common vitiligo (formerly referred to as vitiligo vulgaris). This most common form of vitiligo is characterized by asymptomatic, well-circumscribed, milky-white macules involving multiple parts of the body, usually bilateral and symmetrical in pattern **(figure 4)**. The disease can start at any

site of the body but the fingers, hands, and face are frequently the initial sites ***(Yaghoobin et al., 2011; Ezzedine et al., 2012).*** It was believed to be caused mainly by the autoimmune loss of melanocytes from the involved areas. It is frequently associated with other autoimmune diseases. This indicates the presence of genetically determined susceptibility to not only vitiligo but also to other autoimmune disorders ***(Oiso et al., 2011).***

The course of the disease is unpredictable but is often progressive with phases of stabilized depigmentation ***(Njoo and Westerhof, 2001).*** Cases with more extensive vitiligo vulgaris, involving greater than 30% body surface area, are generally considered unsuitable for transplantation procedures as chances of retention of the pigment are less ***(Faria et al., 2014).***

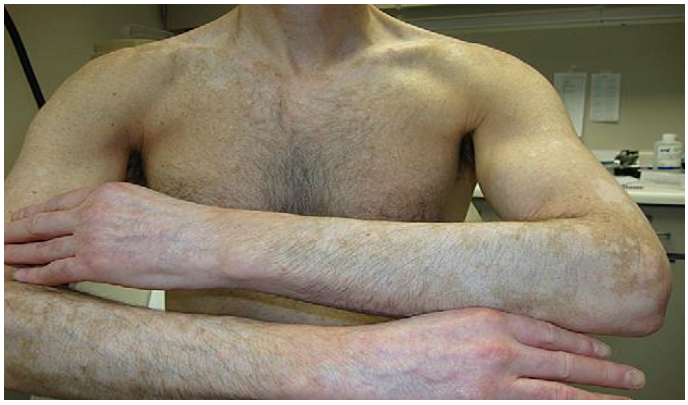

Figure (4): Generalized vitiligo ***(Yaghoobi et al., 2011).***

2) Acrofacial:

In acrofacial vitiligo, the involved sites are usually limited to face, head, hands, and feet ***(Wang et al., 2013).*** It

comprises 3–12% of cases in clinical studies ***(Zhang et al., 2009).***

A distinctive feature is depigmentation of the distal fingers and facial orifices **(figure 5)**. It may later include other body sites, resulting in typical generalized vitiligo ***(Ezzedine et al., 2012).***

Figure (5): Acro-facial vitiligo under wood's light ***(Ezzedine et al., 2012).***

3) Mucosal vitiligo

Mucosal vitiligo typically refers to the involvement of the oral and/or genital mucosae **(figure 6)**. It may present as part of generalized vitiligo when associated with other sites of skin involvement ***(Ezzedine et al., 2012).***

Vitiligo lesions involving the oral and genital mucosa are more resistant to medical therapies, as no melanocyte reservoir

exists in these areas because of absence of hair follicles ***(Mulekar et al., 2007).***

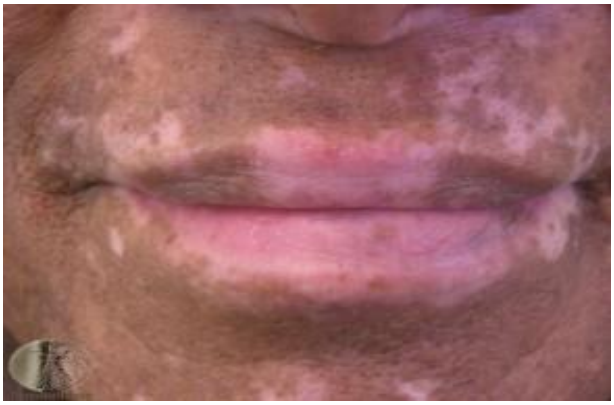

Figure (6): Mucosal vitiligo ***(Ezzedine et al., 2012).***

4) Mixed vitiligo

Mixed vitiligo refers to concomitant occurrence of SV and NSV in the same patient. Usually, SV precedes NSV, though not always **(Figure 7)**. Criteria proposed for mixed vitiligo are as follows: Absence of depigmented areas in a segmental distribution at birth and in the first year of life by Wood's lamp examination excluding nevus depigmentosus ***(Ezzedine et al., 2011).***