# FOCUS ON VITILIGO

**DPC Journal Supplement**

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Aetiopathogenesis of Vitiligo

Katia Boniface

1 University of Bordeaux, CNRS, Immuno ConcEpT, UMR 5164, Bordeaux, France

Key words: vitiligo, melanocytes, keratinocytes, fibroblasts, immune cells, resident memory T cells, cytokines

Citation: Boniface K. Aetiopathogenesis of Vitiligo. Dermatol Pract Concept. 2023;13(4)S2:e2023314S. DOI: https://doi.org/10.5826/dpc.1304S2a314S

Accepted: December 11, 2023; Published: December 2023

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Funding: None.

Competing Interests: Katia Boniface received grants from Calypso Biotech, LEO Pharma, Pfizer, Pierre Fabre, Sanofi, and has a patent on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and three-dimensional model of depigmenting disorder.

Corresponding Author: Katia Boniface: Bordeaux University, CNRS, ImmunoConcept, UMR 5164, F-33000 Bordeaux, France katia.boniface@u-bordeaux.fr

ABSTRACT

Vitiligo is a chronic auto-immune disease characterized by skin depigmentation due to the loss of melanocytes. The better understanding of the disease mechanisms is currently undergoing a significant dynamism, opening a new era in therapeutic development. The pathophysiology of vitiligo has attracted the attention of researchers for years and many advances have been made in clarifying the crosstalk between the cellular players involved in the development of vitiligo lesions. The understanding of the complex interactions between epidermal cells (i.e. melanocytes and keratinocytes), dermal fibroblasts, and immune cells, led to a better characterization of the signals leading to the loss of melanocytes. Recent advances highlighted the role resident T memory cells in the development and recurrence of lesions. This narrative review aims to give an overview of the mechanisms leading to melanocyte disappearance in vitiligo, with a focus on the intercellular interaction network involved in the activation of the local skin immune response.

Introduction

The pathophysiology of vitiligo is complex and involves combinatorial factors (genetic predisposition, environmental triggers, intrinsic melanocyte abnormalities, oxidative stress), leading to an exaggerated activation of the innate and adaptive immune response (Fig. 1) [1]. Genome wide association studies (GWAS) have improved the understanding of the genetic architecture of vitiligo. It is considered that the overall risk of vitiligo linked to genetic determinants is high, corresponding to about 80% of the risk, whereas environmental factors account for 20% [2,3]. Indeed, four large-scale GWAS, three of which were carried out on European and North American populations and one on an Asian (Chinese) populations, identified more than fifty vitiligo susceptibility genes [4–7]. Interestingly, most of these genes are associated with proteins related to innate, adaptive or regulatory immune responses. Others regulate cell apoptosis and some genes are related to proteins regulating melanocyte function. This review discusses how the crosstalk between
epidermal, dermal, and immune cells leads to melanocyte disappearance in vitiligo.

Initiation of the Disease: Bridging Oxidative Stress, Epidermal, Dermal Cells and the Activation of the Innate Immune Response

For many years, it has been considered that melanocytes located in the non-lesional pigmented skin of vitiligo patients are more sensitive to oxidative stress by releasing elevated levels of reactive oxygen species (ROS), associated with an imbalance in the antioxidant system [8]. Keratinocytes and fibroblasts also display increased levels of ROS [9]. This accumulation of ROS leads to several intracellular events such as DNA abnormalities and premature apoptosis that induce the release of several melanocyte peptides as well as abnormal melanocyte function and melanin production [8].

Melanocytes produce pro-inflammatory signals such as damage-associated-molecular patterns (DAMPs) and chemokines, leading to the activation of the immune response and the recruitment of immune cells. Among these danger signals, inducible heat shock protein 70 (HSP70), calreticulin (CRT) or high mobility group B1 (HMGB1) proteins are the most evaluated in vitiligo [10–14]. These DAMPs released in the extracellular environment are likely bridging cellular stress and the autoimmune response directed against melanocytes in vitiligo, and could therefore represent interesting potential targets to prevent the initiation of disease-causing autoimmunity [15]. Indeed, HMGB1 can induce the production of chemokines, such as ligand (C-X-C motif) CXCL16 or interleukin (IL)-8 by epidermal cells (melanocytes and keratinocytes), which are important for the recruitment of immune cells [11]. CRT may induce apoptosis of melanocytes and the release of membrane debris important for immunogenicity [10]. Lastly, several studies from the group of Le Poole emphasized the role of HSP70i in vitiligo [13,16–18], and our group showed its involvement in the activation of innate immunity and the production of type I interferon (IFN) [14].

Keratinocytes also play an important role in the physiopathology of vitiligo. Structural alterations of keratinocytes have been observed in the non-lesional skin of patients, with abnormal thickening of the epidermis due to an increase in the spinous layer [19]. Alterations of basal and suprabasal keratinocytes, in particular vacuolar degeneration and spongiosis, are sometimes found [20]. At the peri-lesional site (at the edge of the lesions, where melanocytes are still present), keratinocytes have the capacity to produce several factors that contribute to the generation of a pro-inflammatory environment, such as stem cell factor (SCF), endothelin-1 (ET-1), and pro-inflammatory cytokines like IL-1β, IL-6, and tumor necrosis factor (TNF)-α. Danger signals produced locally in the skin are responsible for the activation of the pyrin domain of NOD like receptor (NLR) proteins, such as NLRP3, which leads to the formation of an inflammasome and the production of interleukin-1β (IL-1β), a pro-inflammatory cytokine.

Figure 1. Pathophysiological mechanisms of vitiligo. In a genetically predisposed individual and under environmental triggers, epidermal cells (keratinocytes and melanocytes) will release danger signals (e.g.: HSP70), leading to the activation of the innate immune system. IFNγ-producing innate lymphoid cells (ILC1) or IFNα-producing plasmacytoid dendritic cells will induce the production of chemokines, such as CXCL9, CXCL10, or CXCL16 by epidermal and dermal cells. Melanocytes expressing the CXCR3B subunit can be impacted by the interaction with these ligands. Together, these events will induce local activation of resident memory T cells and the recruitment of circulating T cells expressing CXCR3 and NKG2D and producing elevated levels IFNγ and TNFα, leading to the loss of melanocytes and depigmentation.
as NLRP3, an inflammasome activating protein, promoting the secretion of IL-1β and IL-18 [21]. In addition, keratinocytes from vitiligo non-lesional and peri-lesional skin release chemokines involved in the recruitment of T cells in the skin, like CXCL9, CXCL10, and CXCL16. CXCL9 and CXCL10, induced by IFNγ (an important cytokine in the physiopathology of vitiligo), bind to their cognate receptor CXCR3 expressed on immune cells, and most T cells in vitiligo patients skin express CXCR3 [14,22–24]. In addition, Xu et al. recently showed in a mouse model of vitiligo that IFNγ-responsive dermal fibroblasts, through their release of chemokines, are active players in the homing of CD8 T cells to the skin [25].

Another innate inflammatory signature found increased in peri-lesional areas of vitiligo is the IFNα pathway, which contributes to the activation of antigen-presenting cells in the skin and the production of chemokines to reinforce the recruitment of other immune populations at the peri-lesional site [26,27]. IFNα production is linked to the presence of plasmacytoid dendritic cells and induces the release of chemokines such as CXCL9 and CXCL10 by epidermal cells [14,26]. In addition, the presence of innate immune lymphoid type 1 cells (ILC1) in vitiligo skin has been recently demonstrated, which respond to non-specific stimuli and produce significant amounts of IFNγ during the initiation of the disease, leading to early melanocyte apoptosis [28].

**Progression Phase of the Disease: Involvement of a Cutaneous Immune Memory Response**

Following these initial events, vitiligo skin is characterized by the presence of a localized T cell infiltrate close to the epidermis and residual melanocytes, mainly consisting of CD8 T cells. Recent studies highlighted the involvement of resident memory T cells (T RM) in disease pathogenesis [24,27,29–31]. T RM are long-lived memory T cells that persist in tissues like the skin and are characterized by a specific transcriptional program [32,33]. They express characteristic cell surface markers involved in their retention in the tissue, such as CD69, CD103, or CD49a, the latter marker defining a subset of T RM cells with cytotoxic properties [29,34–36]. It is now clear that the micro environment plays a crucial role in the formation and regulation of T RM. Indeed, the expression of CD103 is dependent on transforming growth factor (TGF)-β [36], and a growing number of studies reported the involvement of several pro-inflammatory cytokines involved in T RM homeostasis, such as IL-15, IL-12, IL-18, IL-33, IFNγ, TNFα [32]. The presence of T RM in vitiligo skin is undoubtedly linked to the recurrence of lesions on previously affected anatomical sites that have repigmented following treatment [37], as shown in psoriasis or atopic dermatitis [38–40]. Therefore, owing to their functional role in the pathogenesis of vitiligo, targeting T RM appears as a reliable therapeutic strategy.

**Vitiligo: Mainly a Type 1 Skewed Immune Response**

Analyses of vitiligo peri-lesional and lesional skin revealed upregulation of type-1 associated pathways. Vitiligo is consistently associated with an infiltration of CD8 T cells producing high levels of IFNγ and TNFα. These T cells are characterized by the expression of the receptor CXCR3 that respond CXCL9 and CXCL10, which are highly expressed in the skin of patients [24,41–44]. Targeting the CXCR3-CXCL9 and CXCL10 axis in vitiligo seems to be a promising therapeutic strategy in vitiligo [43,45]. Our group showed that natural killer group 2 member D (NKG2D) defines a subset of highly functional memory CD8 T cells in vitiligo and may represent a potential therapeutic target [46]. This type-1 immune response appears to be a key driver of melanocyte loss in vitiligo and participates in every stage of the pathogenesis. To date, IFNγ and TNFα immune pathways are the most studied in vitiligo. The binding of IFNγ to its receptor induces a signaling dependent of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways, in particular the activation of JAK1/2 and STAT1. Interestingly, JAK inhibition appears to be a reliable strategy to treat patients and ruxolitinib cream (a topical JAK 1 and JAK 2 inhibitor) is now approved both in US and EU for the management of vitiligo [47–49]. IFNγ induces the production of CXCL9 and CXCL10 by keratinocytes, amplifying the inflammation and the recruitment of immune cells expressing CXCR3 which will promote the progression of vitiligo [14]. IFNγ and TNFα also have a direct impact on the function of melanocytes by decreasing the pigmentation process [50–53]. We recently demonstrated that the combined activity of these two cytokines induces the disruption of E-cadherin expression, the main protein responsible for the adhesion of melanocytes to keratinocytes, leading to their destabilization and detachment [53]. In addition, Tulić et al. showed that melanocytes are able to express the B isoform of CXCR3 in response to IFNγ, making them more susceptible to apoptosis in response to CXCL10 [28].

Additional cytokines and signaling pathways may also be involved in vitiligo pathogenesis. For example, elevated levels of IL-17 and IL-23 are found in the serum and/or skin of vitiligo patients, and IL-17 has been reported to regulate melanocyte function and survival [56]. However, targeting IL-17 in vitiligo patients did not show a major benefit [57]. Type-2-related cytokines have been reported increased in vitiligo patients’ blood, and few studies showed an inhibition of melanogenesis in response to IL-4 and IL-13 [58–62]. Our group found that vitiligo skin is also associated with a type-2 immune response and an increased production of IL-13 by T cells [27]. In addition, Jin et al. reported that IFNγ-induced dermal fibroblasts to release CCL2 and CCL8, inducing a type-2 cytokine profile in vitiligo skin lesion [63]. However,
the precise role of type-2 related cytokines in the development of vitiligo remains unclear.

Defects in Immune Regulation During Vitiligo

Like any chronic inflammatory disease characterized by an exaggerated immune response, vitiligo is associated with a disruption of immune regulatory systems. Indeed, GWAS identified a polymorphism of FOXP3 gene, the main transcription factor of regulatory T cells (Tregs), in vitiligo, but also of genes involved in regulation of the immune response, such as CTLA-4 (cytotoxic T lymphocyte antigen 4), IL-10, and TGFβ [3,64,65]. However, it is still unclear whether this defect in the regulation mechanisms results from reduced migration of Tregs into the skin and/or loss of suppressive function of these cells, which would favor the exacerbated effector activity of CD8 T cells [66,67]. Chemokines and their receptors appear critical factors to replenish Tregs in vivo in mice [68]. In addition, Gellatly et al. showed in a vitiligo mouse model that CCR5/CCL5 axis facilitates Tregs migration into the skin and reduced depigmentation instance, enhanced skin expression of CCL22 induced migration of Tregs into the skin and ensure their immunosuppressive function. For instance, enhanced skin expression of CCL22 induced migration of Tregs into the skin and reduced depigmentation in vivo in mice [69]. Hence, therapeutic strategies aiming to restore Tregs abundance and function in the skin may be promising for patients [70].

Conclusion

The development of vitiligo lesions involves a complex cross-talk between epidermal, dermal, and immune cells. Such understanding of the mechanisms leading to the loss of melanocytes led to the identification of several targets and the development of future targeted therapies that will undoubtedly improve the management of the disease.

References


Clinical Features of Vitiligo and Social Impact on Quality of Life

Julien Seneschal\textsuperscript{1,2}

\textsuperscript{1} Department of Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin disorders, Hôpital Saint-André, Bordeaux, France
\textsuperscript{2} University of Bordeaux, CNRS, Immuno ConcEpT, UMR 5164, Bordeaux, France

\textbf{Key words:} vitiligo, mental health, social impact, quality of life

\textbf{Citation:} Seneschal J. Clinical Features of Vitiligo and Social Impact on Quality of Life. Dermatol Pract Concept. 2023;13(4)S2:e2023312S. DOI: https://doi.org/10.5826/dpc.1304S2a312S

\textbf{Accepted:} December 11, 2023; \textbf{Published:} December 2023

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\textbf{Funding:} None.

\textbf{Competing Interests:} Julien Seneschal: received grants and/or honoraria from AbbVie, Bristol Myers Squibb, Calypso Biotech, Eli Lilly, Incyte, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi, Sun Pharmaceuticals, and Viela Bio; and has a patent on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and three-dimensional model of depigmenting disorder.

\textbf{Corresponding Author:} Julien Seneschal M.D, Ph.D., Department of Dermatology, Hôpital Saint-André, CHU de Bordeaux, Bordeaux, France. Bordeaux University, CNRS, ImmunoConce, UMR 5164, 33000 Bordeaux, France. Phone : +33(0)5 36 79 47 05 Fax : +33(0)5 36 79 49 75 E-mail : julien.seneschal@chu-bordeaux.fr

\textbf{ABSTRACT}

\textbf{Introduction}

Vitiligo is the most common cause of depigmentation and its estimated worldwide prevalence ranges from 0.5\% to 2\%. The disease is characterized by the development of white macules resulting from a loss of epidermal melanocytes. The term vitiligo (nonsegmental) is now a consensus umbrella term for all forms of generalized vitiligo. Two other subsets of vitiligo are segmental vitiligo and unclassified/undetermined vitiligo, which corresponds to focal disease and rare variants. A series of hypopigmented disorders may masquerade as vitiligo, and some of them need to be ruled out by specific procedures including a skin biopsy. The skin plays an important role in our interaction with the world and any change in the skin colour can have important psychological consequences. In this line, vitiligo has a major impact on quality of life.

In this review, we will detail the most recent data on the clinical features of vitiligo and its impact on quality of life.

Vitiligo is the most common skin depigmenting disorder resulting from a selective loss of epidermal melanocytes and affects around 0.5-2\% of the world population. Both sexes are equally affected, and there are no apparent differences in rates of occurrence according to phototype or race [1,2]. Twenty five percent of cases are children with disease onset before the age of 10, the age of onset in paediatric series varies from 4 to 8 years. Very early onset, as young as 3 months, is acknowledged. The existence of true ‘congenital vitiligo’ remains controversial [3,4]. In fair-skinned individuals, vitiligo patches
are usually detected only after the first exposure of the skin to sunlight, following the first summer of life. The percentage of segmental vitiligo (SV) is higher in children compared to adults, whatever the ethnic background, suggesting a mosaic skin developmental predisposition. The prevalence of SV in childhood varies from 4.6 to 32.5% in published reports. In addition, besides the recognition of clinical lesions of vitiligo, it is now important to recognize clinical signs of disease that could justify for patients with a progressive disease a treatment to stop the spreading of the disease.

In addition, vitiligo is always associated with major impact on quality of life [5]. This review summarizes classification, clinical aspects, and current knowledge regarding the impact on quality of life of patients affected by vitiligo, a still high unmet disease.

Clinical Features of Vitiligo
Vitiligo is characterized by the progressive loss of melanocytes leaving white patches on the skin. It is usually diagnosed by clinical examination alone supported by Wood’s lamp examination. The differential diagnoses of vitiligo include pityriasis alba, hypopigmented mycosis fungoides, tinea versicolor, idiopathic guttate hypomelanosis, and other hypo- or depigmented disorders. Additionally, the diagnosis of vitiligo could be difficult in patients with fair skin. In cases of uncertain diagnosis, a skin biopsy, mycologic examination, and appropriate blood tests may be needed to exclude a fungal infection, cutaneous lymphoma and other disorders. Routine screening of anti-thyroid antibodies and thyroid function are recommended. The term “vitiligo (non-segmental)” referring to all forms of vitiligo except segmental vitiligo is now proposed. Segmental vitiligo (SV) refers to a clinically unilateral segmental distribution of depigmented lesions. The coexistence of SV plus vitiligo (non-segmental) is called mixed vitiligo. Focal vitiligo, a term that applies to localized macules characterized by loss of melanocytes, was assigned to the category undetermined/unclassified until more definitive classification can be made on clinical grounds (generally after 1–2 years of follow-up).

Vitiligo Subsets
Generalized Vitiligo
This most common form of vitiligo is characterized by white macules involving multiple parts of the body, most often in a symmetrical pattern (Fig. 1). Skin hypopigmentation is usually asymptomatic, but a minority of patients mention preceding mild pruritus (probably due to the inflammation). The disease can start at any site of the body, but the fingers, hands, and face are frequently the initial sites. Depigmentation of scars is a common manifestation of the Koebner’s phenomenon (mechanical induction of the disease, also by friction or chronic pressure by clothing or daily activities). Koebner’s phenomenon is usually contemporary of disease flares [6]. Stable lesions are well demarcated. Mixed vitiligo is a more recently described, mostly paediatric subtype, with segmental involvement preceding typical generalized vitiligo [7]. The presence of leukotrichia and halo nevi have been noted as predictors of passage to mixed vitiligo in patients with SV [8]. Mixed vitiligo may exist in adults but is probably frequently masked by widespread bilateral lesions.

Acrofacial Vitiligo
In acrofacial vitiligo, the involved sites are usually limited to face, head, hands, and feet (Fig 1). A distinctive feature

Figure 1. Clinical features of vitiligo
is depigmentation of the distal fingers and facial orifices. It may later include other body sites, resulting in typical generalized vitiligo. Acrofacial vitiligo was shown to be more frequent in adult onset cases of vitiligo in a large series studies using latent class analysis [9].

**Vitiligo Universalis**

Vitiligo universalis is a rare presentation of vitiligo. It is the most extensive form of the disease and generally occurs in adulthood. ‘Universalis’ is generally used when depigmentation is virtually universal (80–90% of body surface), but some pigmentation may be still present, and hairs partially spared.

**Segmental Vitiligo**

Mono-segmental vitiligo is the most common form of SV, referring to the presence of one or more white depigmented macules distributed on one side of the body, usually respecting the midline (although some lesions may partly cross the mid-line), early follicular involvement (leukotrichia), and rapid development over a few weeks or months, and overall protracted course but secondary extension remains possible in a given segment sometimes years after [10,11]. The aetiology of the SV pattern remains overall elusive. Rarely, multiple segmental lesions occur simultaneously or not distributed either unilaterally or bilaterally. A clear segmental distribution of the lesions with midline demarcation, together with the associated features described in mono-segmental cases (leukotrichia, protracted course), distinguishes this diagnosis versus vitiligo in bilateral cases.

**Unclassified and Rare Variants**

Focal cutaneous or mucosal vitiligo (defined as small isolated patch that does not fit a segmental distribution, and which has not evolved into vitiligo after a period of at least 2 years) should be left within the category undetermined/unclassified vitiligo. Vitiligo punctue/ punctata lesions present as sharply demarcated depigmented punctiform 1- to 1.5-mm macules involving any area of the body, and has to be distinguished histopathologically from guttate hypomelanosis, a common condition with no loss of melanocytes situated on chronically sun exposed sites such as the legs and forearms. Vitiligo minor/hypochromic vitiligo to affect only dark-skinned individuals. ‘Minor’ refers to a partial defect in pigmentation. The relation to true vitiligo comes from pathology and coexistence with more typical vitiligo macules. Cutaneous T cell lymphoma needs to be ruled out by repeated biopsies with molecular studies of clonality, and this diagnosis cannot be made without a long-term follow-up. Follicular Vitiligo refers to a form of generalized vitiligo that primarily involved the pigment cell follicular reservoir with limited skin involvement, contrasting with marked generalized hair whitening.

**Clinical Signs of Disease Activity**

Recently it has been defined different clinical signs associated with the progression of the disease. Several visible clinical skin manifestations in vitiligo are reported in relation to disease progression such as inflammatory borders, Koebner phenomenon, hypochromic areas/ borders and confetti-like depigmentation [12]. The presence of these clinical markers in patients with vitiligo has been linked to poor prognosis, rapid disease progression and inadequate response to therapies. Confetti-like depigmentation was first described by Sosa JJ and defined as the presence of several grouped 1 to 5-mm depigmented macules, usually located at the border of an existing lesion [13]. Therefore, these signs are important to recognize to start as soon as possible treatment that could stop the spread of the disease (Fig. 2).

**Social Impact on Quality of Life**

Skin plays an important role in our interaction with the world, and skin colour is an important element in our interaction with the world. In this sense, any change in skin colour can have important psychological consequences. In patients with vitiligo, quality of life and disease burden can be measured by generic dermatology instruments such as the Daily Life Quality Index (DLQI). Although generic instruments such as the DLQI can provide a general picture of impaired quality of life, they generally fail to detect nuances in the way patients manage the overall burden of vitiligo. In this context, over the last decade, several specific scores to measure the individual impact of the disease have also been developed, such as the Vitiligo Impact Scale (VIS), the Vitiligo Quality Of Life (VitiQoL) or the Vitiligo Impact Patient Scale (VIPs) [14]. Of all these scores, only the VIPs considers the patient’s phototype, which is a major factor in the experience of the disease [15]. In the late 1970s, Porter et al. first reported the major impact of vitiligo on patients’ quality of life and there is now strong evidence that patients with vitiligo are negatively affected in their sexual relationships [16].

In addition, several studies have shown that adult patients with generalized vitiligo experience a decrease in quality of life comparable to that of patients with other skin diseases such as atopic eczema and psoriasis [5]. Indeed, many people are afraid and uncomfortable when they come into contact with people with vitiligo, thus discriminating against these patients. Vitiligo patients also complain that they do not receive enough support from their doctors. More recently, in 2005, a survey of members of the United Kingdom Vitiligo Society showed that over 50% of respondents said that vitiligo had a significant impact on their quality of life. In this study, finding an effective and long-lasting treatment was the top priority for the patients who responded to the survey and who had the most severe forms. Only a small number of
that people with vitiligo suffer from low self-esteem, social stigma, shame, avoidance of intimacy, anxiety, depression, adjustment disorders, fear, suicidal ideation and other psychiatric comorbidities [24]. In an internet survey of children aged 0-17 years and their families, the deterioration in quality of life increased with age: more than 90% of teenagers (15-17 years) were bothered by vitiligo compared to 50% of children aged 0-14 years [22]. The localization of the disease vitiligo on the face, arms and legs was found to be the most distressing and was associated with teasing and bullying. Finally, depression and anxiety in children were reported by 26% and 42% of parents and caregivers respectively [25].

Conclusion

Vitiligo is a common disease with an estimated global prevalence of 1%. Its impact on quality of life and self-esteem is considerable and long-lasting, with possible repercussions in adulthood for children with the disease. In this context, it is important to listen to patients and to take charge of their psychological suffering by not hesitating to offer psychological care.

References


Vitiligo: Current Therapies and Future Treatments

Julien Seneschal¹², Katia Boniface²

¹ Department of Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin disorders, Hôpital Saint-André, Bordeaux, France
² University of Bordeaux, CNRS, Immuno ConcEpT, UMR 5164, Bordeaux, France

Key words: vitiligo, management, treatment

Citation: Seneschal J, Boniface K. Vitiligo: Current Therapies and Future Treatments. Dermatol Pract Concept. 2023;13(4)S2:e2023313S. DOI: https://doi.org/10.5826/dpc.1304S2a313S

Accepted: December 13, 2023; Published: December 2023

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Funding: None.

Competing Interests: Julien Seneschal: received grants and/or honoraria from AbbVie, Bristol Myers Squibb, Calypso Biotech, Eli Lilly, Incyte, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi, Sun Pharmaceuticals, and Viela Bio; and has a patent on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and three-dimensional model of depigmenting disorder.
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Authorship: Both the authors have contributed significantly to this publication.

Corresponding Author: Julien Seneschal, Department of Dermatology, Hôpital Saint-André, CHU de Bordeaux, Bordeaux, France.
Bordeaux University, CNRS, ImmunoConcept, UMR 5164, 33000 Bordeaux, France. Phone: +33(0)5 56 79 47 05 Fax: +33(0)5 56 79 49 75 E-mail: julien.seneschal@chu-bordeaux.fr

ABSTRACT

The current management of vitiligo remains challenging; however, different strategies can be proposed to patients with a good efficacy in many cases. First, it is important to identify patients in the active phase of the disease because treatment should start as soon as possible to halt its progression. For patients with a stable disease, the treatment strategy is now well-stratified and is based on a combination of phototherapy (natural or in a cabin) and topical immunomodulatory agents. Surgical treatments are useful for localized and stable vitiligo, as well as for segmental vitiligo. Depigmentation remains indicated in very extensive forms. The recent approval of topical ruxolitinib cream in both the US and Europe brings new approaches for the management of vitiligo and paves the way for the development of new topical or oral targeted drugs.

Introduction

Vitiligo is a common chronic depigmenting skin disease that can have a significant impact on the quality of life of those affected. Consequently, there is often a high demand for treatment among patients. Advances in understanding the pathomechanisms of vitiligo led to the development of targeted therapies. For example, ruxolitinib, a topical JAK1/ JAK2 inhibitor, is now approved for the management of vitiligo both in the US and Europe. This review aims to provide...
a practical guidance on managing patients with vitiligo and to explore potential future therapies currently in development. Recent worldwide expert recommendations for the diagnosis and management of vitiligo have been recently published [1,2]. Part 1 of the recommendations provides a practical algorithm for the treatment of vitiligo.

Objectives of Treatments

Treatment strategies depend on several clinical characteristics, such as disease subtype, the extent of vitiligo, and disease activity. These factors should be systematically assessed before deciding on a specific therapy. The management of vitiligo should encompass three main complementary objectives: 1) halting disease progression, 2) inducing repigmentation, melanocyte regeneration and proliferation, and 3) maintaining repigmentation and preventing disease recurrence.

Treating Patients with Active Disease

Vitiligo is a chronic condition that often progresses in flare-ups. It is impossible to predict the long-term evolution of vitiligo, and to date there are no reliable biological markers of activity. However, clinical signs of disease activity have been identified, such as inflammatory borders, the Koebner phenomenon, hypochromic areas/borders, and confetti-like depigmentation. It is essential to detect active forms of vitiligo because a treatment aiming to block flare-ups must be initiated urgently [3–7].

While data are primarily based on open or retrospective studies, it is now widely accepted that the treatment for patients with highly progressive disease should combine systemic therapies and phototherapy [8]. To date, the systemic therapy mainly relies on mini-pulses of systemic steroids for 3 to 6 months (e.g. methylprednisolone 16mg or dexamethasone 5mg) two consecutive days in adults, the dose should be adapted for children) [9]. For children in the growth phase, a paediatric advice should be given after 3 months of treatment. Systemic steroids should be combined with phototherapy: e.g Narrow band UVB 2-3 times/week for 6 months. This combination blocks relapses in over 80% of cases. In small children, phototherapy cannot be used and the mini-pulses are used as a monotherapy. Depending on the season, moderate but regular exposure to the sun is recommended to stimulate repigmentation.

Treatment for Patients with a Stable Disease

With current strategies, complete or near complete repigmentation could be achieved (e.g. 70 to 80% of repigmentation of lesions located on the face; 50% of repigmentation of lesions located on the body; hands and/or feet remain difficult to treat). Importantly, the treatment should be evaluated after at least 6 months. Indeed, it can take between 6 to 24 months of treatment to achieve significant repigmentation. Patients must be clearly warned that the treatment is long and often tedious, as many patients stop the treatment after 1 to 2 months without seeing any results.

Topical immunomodulatory treatments are important. On the face and other sensitive areas, tacrolimus 0.1% (including in infants) or pimecrolimus 1% should be used twice a day. Unfortunately, this prescription is still off-label despite numerous very robust methodological studies [10,11]. On the body, a strong topical steroid can be used instead of tacrolimus, once a day, preferably in the evening, and sequentially (e.g. 5 days a week) [12]. The topical JAK-inhibitor ruxolitinib is the first treatment approved for vitiligo both in US and Europe for the management of vitiligo affecting the face and less than 10% of the body surface area for adults and adolescents (≥12 years old). Two randomized, double blind, phase III studies were conducted in 674 patients. Patients applied ruxolitinib cream 1.5% twice a day. Response rates were much better than in the placebo group, with 50.3% and 74.6% of patients achieving a Facial-VASI (F-VASI) 75 and 50, respectively, at week 52. Moreover, 51.1% of patients achieved a total VASI (T-VASI) of 50 at week 52 [13]. Head and neck responded the best, followed by upper and lower limbs, and by trunk. Hands and feet remained the most difficult areas to repigment. Interestingly, all the areas, excepted for hands and feet, did not reach a plateau, suggesting that longer treatment will allow further improvement that was confirmed in long-term extension studies. Adverse events were mainly mild or moderate. The most common adverse events were aceiniform reactions located on site of the application as well as pruritus. Clinical trials are ongoing to see whether the efficacy could be better in combination with UV lights (NCT05247489).

Indeed, currently, without UV (whether natural, cabin, lamp or laser), the repigmentation is long to obtain. If possible, UVB should be preferred to PUVA therapy. For localized vitiligo, excimer lamps and lasers are of great interest [14–17]. It is important to note that there are now narrow spectrum UVB lamps available that are finally affordable for patients [18,19]. These lamps allow home phototherapy and are very useful for localized lesions of vitiligo. Sun exposure can be offered during the summer season. Patients should be advised to expose moderately themselves at least 3 or 4 times a week, without sunscreen, until their skin turns pink.

A combination of sun exposure with immunomodulating agents is crucial to achieve good repigmentation. There are now well-established recommendations for using phototherapy in patients with vitiligo [17]. Regarding the sun exposure in patients with vitiligo, it is important to note that patients with vitiligo have a lower risk of developing skin cancer and in particular a lower risk of developing melanoma. There is also no increased risk of skin cancer with narrow-spectrum
UVB phototherapy in vitiligo (up to at least 400 sessions). In addition, no increased risk of skin cancers has been shown if NB-UVB is combined with tacrolimus [20–22].

**What is the Place of Melanocyte-Grafting?**
Transplants have two main indications in vitiligo. They can be proposed after the failure of medical treatments for vitiligo that has been stable for at least 12 months and segmental vitiligo.

Several techniques have been described: – epidermal suspensions; – epidermal suction and then grafting; – thin skin grafting; – mini-grafting; – in vitro culture of keratinocyte and melanocyte suspensions. Epidermal suspensions are preferred and now approved commercial tissue-dissociation kits can be used in the clinic [23,24].

**How can Recurrences be Prevented?**
Almost 50% of vitiligo lesions recur in the first year after repigmentation without a maintenance therapy [25]. For instance for the face, it has been shown than the use of tacrolimus 0.1% twice weekly (without the need of sun exposure) reduces the risk of relapse from 40% to 9.7% [26]. Topical steroids on the same schedule are probably also effective but this has not been yet demonstrated. For patients with a larger extent of the disease, the use of NB-UVB once or twice a month as a maintenance treatment could be discussed [17]. However, data supporting this procedure are still lacking. Some systemic treatments currently under development may be of interest to block the recurrence of vitiligo.

**When and How to Propose Depigmentation?**
Depigmentation can be discussed for patients with depigmented areas affecting more than 50% of the body. Chemical depigmenting products such as MEBH (hydroquinone monobenzylether) are no longer available in most of European countries. Depigmenting lasers have shown similar approximately a 70% success rate after 1 to 3 sessions. Maintenance sessions after the summer are often necessary, especially on light exposed areas such as the face. For small areas, cryotherapy is an interesting option [27,28].

**Future Therapies in Development**
Vitiligo patients can be strongly encouraged to participate in the latest clinical trials to promote the development of new and more efficient therapies. Besides the approval of topical ruxolitinib both in US and Europe, the oral JAK inhibitors baracitinib (a JAK1/2 inhibitor), upadacitinib and povoricitinib (JAK1 inhibitors are currently being tested in phase II ongoing trials. Ritlecitinib (a JAK3/TEC inhibitor) was recently evaluated with different doses in a phase II trial that included 364 patients [29]. After 24 weeks, the proportion of F-VASI change from baseline was significantly different in the ritlecitinib 50 mg group compared to placebo for the with (-21.2% vs 2.1%, P<0.001). Strategies to target IL-15 or its receptor CD122 to inhibit the generation and the maintenance of skin resident memory T cells demonstrated durable treatment responses in a pre-clinical mouse model of vitiligo and clinical trials using this strategy are underway [30]. Blocking the initiation of the disease could be also an important step for future therapies in vitiligo. HP70i seems to be a critical Danger Associated Molecular Pattern (DAMP) important for the initiation of the disease. Blocking HP70i activity might offer a good strategy as shown in pre-clinical animal models [31–33]. Preventing melanocyte detachment by using matrix metalloproteinase-9 inhibitors could also be effective [34]. Recent data suggest a dysbiosis in the skin and the gut of vitiligo patients. Modulating the vitiligo microbiome offers potential new strategies [35]. In addition, to induce a better repigmentation, it will be important to combine topical and/or oral immunomodulators with strategies that will promote the differentiation and proliferation of melanocyte stem cells in vitiligo lesions, especially located on acral areas or in areas with poliosis [36]. In this line, the WNT signaling, which is repressed in depigmented skin of vitiligo patients, may be an important pathway to target to induce melanocyte differentiation.

**Conclusion**
Patients with vitiligo should be informed on therapeutic options available to treat their conditions. Topical ruxolitinib cream is now approved for vitiligo and this will open the development of other topical and/or systemic treatments for the disease. It is now important to recognize patients with progressive disease that will require urgent treatment to stop the spreading of the disease.

**References**


Vitiligo: Epidemiology and Economic Impact

Luigi Naldi¹, Adriano Pagani², Chiara Alduini²

1 UOC Dermatologia, Ospedale San Bortolo, Vicenza, Centro Studi GISED, Bergamo
2 Kearney, Milan

Key words: vitiligo, epidemiology, mental health, social cost

Citation: Naldi L, Pagani A, Alduini C. Vitiligo: Epidemiology and Economic Impact. Dermatol Pract Concept. 2023;13(4)S2:e2023315S.
DOI: https://doi.org/10.5826/dpc.1304S2a315S

Accepted: December 11, 2023; Published: December 2023
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Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
Corresponding Author: Chiara Alduini, Kearney, Milan, Italy. Email: chiara.alduini@kearney.com

ABSTRACT

Introduction: Vitiligo is an acquired disorder of pigmentation, characterized by the development of white patches on the skin, often with a typical symmetrical distribution and progressive extension [1,2]. Although vitiligo does not cause direct physical impairment, it can produce a relevant psycho-social burden. Despite this burden, effective treatments are lacking, emphasizing the need for new therapeutic options.

Objectives: The aim of this study was to systematically scan the scientific literature for studies dealing with vitiligo epidemiology. Additionally, the study aimed to assess the social costs of vitiligo, ultimately raising awareness about the societal impact of the condition. The focus was on Italian data.

Methods: Our research employed a comprehensive methodology. For the epidemiology, we systematically searched PubMed database up to October 2023 and complemented the analysis with Real World Evidence. For social costs, we conducted an in-depth literature review, administered a web-survey to 20 Italian dermatologists and conducted an equivalent number of interviews during the same period in March 2022.

Results: The data suggest that in Italy the prevalence of vitiligo increases with age, and it varies from 0.19% (age 18-21) to 0.6% (age >45) [3,4]. We estimated 152,000 patients diagnosed with Non-Segmental Vitiligo (NSV) in Italy; based on Body Surface Area (BSA), 33% are Not Severe, 31% Mild, 27% Moderate/Severe, 9% Very Severe. The yearly social costs of vitiligo amount to €0.5Bln.

Conclusions: There is a remarkable association of vitiligo with anxiety and depression [5,6,7,8,9], and Mental Health is associated with 30% of social costs. Moreover, vitiligo social costs distribution highlights inequity, with patients bearing 55% of them.
Introduction

Vitiligo is a chronic autoimmune depigmenting skin disease that results in patchy loss of skin color due to the progressive destruction of melanocytes [1,10]; it is now widely accepted that vitiligo has an autoimmune nature. This condition is characterized by extended periods of stability interspersed with shorter periods of accelerated depigmentation [11]. Treatment remains a challenge in dermatology, as available options produce limited results [12,13].

Vitiligo is a prevalent global skin condition which affects equally both genders, though slightly more prevalent in females, and more than 60% of patients experienced disease onset before the age of 30 [14,15].

There are two main clinical phenotypes [16]: Non-Segmental vitiligo (NSV) and Segmental vitiligo (SV). NSV is the most common form, characterized by symmetrical lesions on both sides of the body, progressing slowly and unpredictably.

Vitiligo is frequently associated with various autoimmune comorbidities such as hypothyroidism and rheumatoid arthritis [17].

The psychological impact is substantial, negatively affecting patients’ quality of life (QoL) and Mental Health [5,6,7,8,9,18,19]. Indeed, the stigma associated with vitiligo impacts personal lives and productivity, leading to poor self-acceptance and psychological distress [20]. Everyday activities are disrupted, causing considerable time and energy waste for patients and their caregivers. Patients commonly experience depression, anxiety, stigmatization, hopelessness, and loss of self-esteem [20,21].

Despite the substantial burden it places on individuals, there is still a notable unmet need for effective treatments, leaving patients frustrated and hopeful for the development of efficacious options.

Objectives

The goals of the study were to determine the prevalence of vitiligo in Italy, segment patients to understand treatment adoption and behavior, and assess the social costs associated with the condition. Moreover, the aim was to shed light on the economic and societal burdens of vitiligo in Italy.

Methods

Our research utilized a comprehensive methodology, encompassing web-surveys involving 20 Italian dermatologists (i.e., “Medical Survey”) in March 2022, interviews with an additional 20 dermatologists during the same period, and an extensive desk research that scrutinized over 100 publications, articles, and industry reports. In particular, data collection included a broad range of sources, including Real-World Evidence, scientific publications, public entities’ websites (e.g., INPS, GU (Gazzetta Ufficiale)), scientific guidelines, national and regional NHS tariffs, statistics institutes (e.g., ISTAT, EUROSTAT), surveys, interviews, as well as information from company websites and the medical press.

Epidemiology

We systematically searched PubMed database up to October 4, 2023, with the following key words: epidemiology, prevalence, incidence, co-morbidities, risk factors. A total of 761 papers were retrieved and, after an eligibility assessment, only 82 were maintained. Out of these papers, 12 were systematic reviews summarising various aspects of the vitiligo epidemiology [5-9,25-28], and another 8 studies presented data on the epidemiology of vitiligo in Italy [3,4,29-35]. To avoid repetition and redundancy, we decided to focus on the above-mentioned studies only, i.e., systematic reviews and Italian data.

We then complemented the analysis through a bottom-up approach, using Real-World Evidence [36]. Lastly, we established patient classes for Non-Segmental vitiligo (NSV) based on clinical and demographic characteristics and validated these classifications through expert interviews.

Social Cost

We assessed both healthcare and non-healthcare costs associated with vitiligo. Among healthcare costs, we examined three components:

- **Vitiligo Treatment**: through the Medical Survey, we investigated the treatment behavior within distinct patient classes, specifically focusing on topical treatments, phototherapy, depigmentation, and surgery. We further quantified the costs associated with each treatment, using publicly available sources. Both NHS and patient costs were considered.

- **Autoimmune Comorbidities**: our study delved into the prevalence of autoimmune comorbidities among vitiligo patients, including conditions such as hypothyroidism, rheumatoid arthritis, and inflammatory bowel disease. For each of these comorbidities, we examined literature on both direct and indirect associated costs.

- **Mental Health Conditions Assessment**: we explored the prevalence of Mental Health comorbidities, such as depression and anxiety, in vitiligo patients and their caregivers, as reported in the literature.

On the non-healthcare cost front, we assessed two components:

- **Non-Drug Products**: through Medical Survey, we examined the usage of non-drug products (e.g., make-up/concealer, self-tanners, sunscreen) within different patient...
classes. Other direct costs were also considered (e.g., transportation expenses).

- **Indirect Social Costs**: our study included an estimation of the time allocated for treating vitiligo and Mental Health comorbidities within each patient class. We also evaluated the influence of Mental Health comorbidities on employment status.

**Results**

**Epidemiology**

Here we present eight Italian studies with a clear epidemiologic design [3,4,29-35].

In the *Praktis study*, conducted between March 1, 2003, and April 30, 2004, a random sample of 12,483 Italian subjects aged 45 or older was collected and interviewed, showing a 0.6% lifetime prevalence of physician-diagnosed vitiligo, with no difference according to gender and an increasing prevalence with age [29].

The *Epienlist project*, carried out by the Department of Dermatology at the Italian Navy Hospital in Taranto, examined 23,468 potential conscripts in southern Italy, aged 18-21. Those with skin lesions were referred to the hospital for diagnosis. The point prevalence of vitiligo was 0.19% [3]. Quality of life was assessed for 40 vitiligo patients, with a mean Dermatology Life Quality Index (DLQI) score of 1.82 [33]. Analysis revealed that only lesions on the hands (OR: 6.32) and face (OR: 5.03) significantly influenced the mean DLQI.

A survey of quality of life was conducted on 181 consecutive vitiligo patients at a single institution in Rome, using the Skindex-29 tool [30]. The problems more frequently experienced were worry of the disease getting worse (60%), anger (37%), embarrassment (34%), depression (31%).

Another survey of quality of life using DLQI was conducted on a sample of 161 vitiligo patients referred to 9 dermatological departments in Italian hospitals [34]. The mean total DLQI score was 4.3 (SD±4.9; range: 0-22). In multivariate analysis, DLQI >5 was associated with female gender, stability of the disease and involvement of the face at disease onset.

In a survey conducted during spring 1997, a total of 3,179 schoolchildren attending secondary schools in Italy were assessed through a questionnaire filled in by their parents [31]. The reported prevalence of vitiligo was 0.06%.

The *EDEN Fragrance study* enrolled 2,035 randomly sampled individuals aged 18 or older in Italy. Clinical examinations and patch tests were conducted. The lifetime prevalence of vitiligo was 0.4%, with no significant gender difference [35].

The prevalence of vitiligo in Italy, as determined by the studies, falls within the range of 0.19%-0.6%, increasing with age.

In addition, an Italian ReS Real-World Evidence study [36] was considered. This study examined the number of patients undergoing phototherapy treatment for vitiligo from 2013 to 2018 and revealed that 0.06% of the patient population received such treatment during that period. Employing a bottom-up methodology, we expanded the study’s scope to incorporate patients who underwent phototherapy prior to 2013 or received alternative treatments, to ensure a complete understanding of the vitiligo-diagnosed population. We then added undiagnosed cases (41%) [35] to derive a lifetime vitiligo prevalence rate of 0.55%, which is in line with that reported by literature.

Considering that only 15% of vitiligo cases are Non-Segmental vitiligo (NSV) [37-40], we estimated a total of 279,000 NSV patients in Italy in 2022. Among these, 152,000 received a diagnosis, with 33% classified as having BSA <0.5% (Not Severe at all), 31% with BSA 0.5%-3.5% (Mild), 27% with BSA 3.5%-10% (Moderate/Severe), and 9% with BSA >10% (Very Severe) [41].

**Vitiligo Treatment Cost**

The costs of vitiligo treatment include all direct medical expenses, including therapies, examinations, laboratory tests, and supplements. NSV treatment rate varies among patient segments. Treatment rate tends to be higher in more Severe forms of NSV: only 35% of Not Severe NSV patients receive treatment compared to 84% of Very Severe NSV patients. Within the same Moderate-Severe segment, adolescents and females exhibit a relatively higher treatment rate (81% and 80% respectively) compared adult males (70%).

For each patient class, treatment preferences were examined through the Medical Survey: preferred options for cases of lower severity included topical corticosteroids and calcineurin inhibitors, while in Moderate-Severe cases, phototherapy and systemic corticosteroids were preferred (Figure 1).

To compute costs, we identified the most used molecules and their average therapeutic regimens, and we distinguished between costs in private and public settings (Table 2). According to the Medical Survey, 49.5% of patients are treated in public, and 50.5% in private settings. Then, considering the specific needs of each class of NSV patients, we added costs for dermatologist and nutritionist examinations, blood/urine tests, and supplements.

Total medical costs for NSV patients amount to €80Mln and the large majority (95%) is covered by the patient. Costs consist of treatments (35%) and supplements (38%), followed by medical examinations (23%) and lab tests (4%). The annual treatment cost per patient ranges from €208 for Not Severe cases to €906 for Moderate/Severe adolescents.

**Autoimmune Comorbidities**

In a retrospective study, 15.3% of patients with vitiligo had one or more significant comorbid autoimmune condition,
Table 1. Summarization of data from relevant Italian studies.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Publication</th>
<th>Focus</th>
<th>Study size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naldi [29]</td>
<td>2004</td>
<td>Lifetime prevalence</td>
<td>Random sample of 12,483 Italian citizens aged &gt;45</td>
<td>Lifetime prevalence 0.06% with no difference based on age and sex</td>
</tr>
<tr>
<td>Ingordo [3]</td>
<td>2007</td>
<td>Point Prevalence</td>
<td>23,468 conscripts in southern Italy, aged 18-21</td>
<td>Point prevalence 0.19%</td>
</tr>
<tr>
<td>Sampogna [30]</td>
<td>2008</td>
<td>Quality of life</td>
<td>181 consecutive vitiligo patients at a Roman institution, using Skindex-29 tool, 12-item General Health Questionnaire</td>
<td>Problems frequently experienced: worry of getting worse (60%), anger (37%), embarrassment (34%), depression (31%). The prevalence of patients with probable depression or anxiety was 39%</td>
</tr>
<tr>
<td>Naldi [31]</td>
<td>2009</td>
<td>Risk factors and diseases associated with atopic dermatitis</td>
<td>3,179 schoolchildren aged 12-17 years</td>
<td>Lifetime prevalence of vitiligo 0.6%</td>
</tr>
<tr>
<td>Ingordo [32]</td>
<td>2011</td>
<td>Autoimmunity in vitiligo</td>
<td>40 conscripts with vitiligo systematically assessed for autoantibodies and history of immune-related disease</td>
<td>Circulating autoantibodies detected in 42.5% of subjects</td>
</tr>
<tr>
<td>Ingordo [33]</td>
<td>2012</td>
<td>Quality of life</td>
<td>40 conscripts with vitiligo assessed through DLQI</td>
<td>Mean total DLQI score 1.82 (SD± 2.95; min/max: 0-13). The localization on the hands (OR:6.32) and on the face (OR:5.03) influenced significantly the mean DLQI</td>
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<tr>
<td>Ingordo [34]</td>
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<td>Quality of life</td>
<td>161 vitiligo patients referred to dermatological departments in Italy assessed by DLQI</td>
<td>DLQI score 4.3 (SD±4.9; range: 0-22). In multivariate analysis, DLQI &gt;5 was associated with female gender, stability of the disease over time and involvement of the face at disease onset</td>
</tr>
<tr>
<td>Svensson [35]</td>
<td>2018</td>
<td>Lifetime Prevalence of vitiligo in a survey on contact dermatitis</td>
<td>Random sample of 2,035 people aged &gt;18 in Bergamo</td>
<td>Lifetime prevalence of vitiligo 0.4% with no significant difference according to gender</td>
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</tbody>
</table>

Figure 1. NSV Treatment Preference by Patient Class (%)
Major Depressive Disorder (MDD) and anxiety (referred to as Generalized Anxiety Disorder, Social Phobia, Specific Phobia, Post-Traumatic Stress Disorder, Agoraphobia, Agoraphobia with Panic Disorder and Panic Disorder) were the most reported. Moreover, patients with vitiligo recur to psychotherapy more often than the general population. We argue that the cost of mental health issues can be part of the overall cost of vitiligo. This is because the increased psychological distress in this group mostly arises from the difficulties caused by the disease itself. Therefore, we collected literature evidence for direct costs of depression (i.e., costs for residential structures, psychiatry-related tests, hospitalizations, antidepressants [55, 56]), costs for anxiety with hypothyroidism and rheumatoid arthritis being the most common [17]. Vitiligo patients incur direct and indirect costs due to autoimmune comorbidities [42-53]. Direct costs include healthcare and non-healthcare costs (e.g., inpatient care, drug costs, tests, transportation). Indirect costs include productivity losses due to morbidity/mortality, borne by the individual, family, society, or the employer (e.g., sick leave, early retirement). Indirect costs were assessed by the human capital approach (HCA) and the friction cost approach (FCA).

**Mental Health Costs**

According to a systematic review on psychosocial effects of vitiligo [3,15,23,54,55], disorders including or related to Major Depressive Disorder (MDD) and anxiety (referred to as Generalized Anxiety Disorder, Social Phobia, Specific Phobia, Post-Traumatic Stress Disorder, Agoraphobia, Agoraphobia with Panic Disorder and Panic Disorder) were the most reported. Moreover, patients with vitiligo recur to psychotherapy more often than the general population. We argue that the cost of mental health issues can be part of the overall cost of vitiligo. This is because the increased psychological distress in this group mostly arises from the difficulties caused by the disease itself. Therefore, we collected literature evidence for direct costs of depression (i.e., costs for residential structures, psychiatry-related tests, hospitalizations, antidepressants [55, 56]), costs for anxiety

<table>
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<th>Table 2. NSV treatment options costs (€, yearly).</th>
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<tr>
<td>Overall cost</td>
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<td>-----------------</td>
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<tr>
<td>Induction therapy CS systemic (± TCS)</td>
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<tr>
<td>Induction therapy TCS</td>
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<tr>
<td>Induction therapy TCI</td>
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<tr>
<td>Maintenance therapy TCS (lower dose)</td>
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<tr>
<td>Maintenance therapy TCI (lower dose)</td>
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<tr>
<td>UVB phototherapy (e.g., NB-UVB, excimer laser)</td>
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<tr>
<td>UVB phototherapy + TCS or TCI</td>
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<tr>
<td>PUVA</td>
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<tr>
<td>Candidate for surgery (scheduled/operated)</td>
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<td>Depigmentation</td>
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<th>Table 3. Disease costs for selected autoimmune diseases (€, yearly).</th>
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<tr>
<td>Overall cost</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<td>Inflammatory bowel disease</td>
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<td>Lymphoma</td>
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<td>Systemic lupus erythematosus</td>
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<td>Seronegative arthritis</td>
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<td>Idiopathic thrombocytopenic purpura</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Pernicious anemia</td>
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<td>Myasthenia gravis</td>
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<th>Table 4. Direct costs associated to Mental Health.</th>
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<tr>
<td>Overall cost</td>
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<tr>
<td>Depression treatment</td>
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<tr>
<td>Overall cost</td>
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</tr>
<tr>
<td>Anxiety treatment</td>
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<tr>
<td>Psychotherapy session</td>
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</table>
value of the HC is approximated by the value of an individual's earning, so that the period of absence from work due to illness/treatment is considered and valued by the achievable gross income [59]. The HC method does not address the issue of the categories not receiving any income (typically stay-at-home spouses, unemployed and students) [60] and their inclusion in indirect costs computation is at the researcher's discretion. To address the limits of HC method, in this study we valued the “unemployed lost time” at the value of governmental unemployed benefit (NASpI [61]); “Inactive caregivers’ time” at the value of minimum domestic labor wage; “Time lost out of working time for vitiligo treatment” (e.g., ointment application, make-up) at the value of willingness to pay for an additional hour of leisure time vs. unpaid work [62], assuming that the burden of treatment is comparable to unpaid work. The data for this section comes from scientific publications, public entities’ websites (e.g., INPS), statistics institutes (e.g., INSTAT).

Our analysis shows that the indirect costs associated to vitiligo amount to €91Mln/year: 30% of this cost (€31Mln) is associated to Mental Health (for either productivity loss related to treatment time or unemployment). The annual indirect social cost per diagnosed patient ranges from €288 for Not Severe cases to €1,182 for Moderate-Severe older males.

Conclusions

In summary, data indicate that vitiligo prevalence increases with age in Italy, ranging from 0.19% at 18-21 years to 0.6% after age 45. Real World Evidence-based prevalence was estimated at 0.55%. These figures align with the findings reported in systematic reviews and recent studies.

Analyzing five cost components, the annual social cost of vitiligo in Italy is €500 million, with costs per patient ranging from €2,200 to €4,600/year. Patients bear 55% of the cost, the NHS covers 18%, and 27% is borne by society. This distribution results in significant inequity, with over half of the social cost being paid directly by patients or caregivers.
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Vitiligo: Unmet Need, Management and Treatment Guidelines

Angelo Valerio Marzano\textsuperscript{1,2}, Silvia Alberti-Violetti\textsuperscript{1,2}, Carlo Alberto Maronese\textsuperscript{1,2}, Gianluca Avallone\textsuperscript{1,2,3}, Claudio Jommi\textsuperscript{4}

1 Dermatology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy
2 Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
3 Department of Medical Sciences, University of Turin, Dermatology Clinic, Turin, Italy
4 Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy

Key words: vitiligo, unmet need, guidelines, clinical pathway


Accepted: December 11, 2023; Published: December 2023

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Funding: None.

Competing Interests: Angelo Valerio Marzano reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer-Ingelheim, Novartis, Pfizer, Sanofi, Incyte and UCB. The other authors report no conflicts of interest.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Angelo Valerio Marzano. Dermatology Unit - Via Pace, 9, 20122 Milan, Italy. Tel. +39 0255034717; fax: +39 0255035236; e-mail: angelo.marzano@unimi.it

ABSTRACT Vitiligo is a chronic depigmenting disorder characterized by characteristic, non-scaly, chalky-white skin macules and patches, due to the loss of skin pigment. Its exact pathogenesis is still not fully understood but it seems to be an autoimmune disease where the combination of genetic, environmental, and immune factors contributes to the destruction of melanocytes in the epidermis. Vitiligo is classified into different types based on its clinical characteristics and distribution patterns. The two main forms of vitiligo are non-segmental vitiligo (NSV) and segmental vitiligo (SV). NSV is the predominant form, characterized by symmetrical skin patches, that tend to evolve over time. In contrast, SV has unilateral or band-shaped lesions that progress rapidly but often stabilize early. Herein, current unmet needs in terms of psychosocial consequences and relative lack of valid therapeutic approaches are critically analyzed and put in perspective in the Italian prescribing scenario. Finally, available management guidelines are illustrated and briefly compared, to provide context for upcoming treatment options.
Introduction

Vitiligo is a chronic depigmenting skin disorder characterized by typical non-sclay, chalky-white patches, due to loss of skin pigment. The exact pathogenesis is still not fully understood but it seems to be an autoimmune disease where the combination of genetic, environmental, and immune factors contributes to induce the destruction of melanocytes in the epidermis [1].

Vitiligo is classified into different types based on its clinical characteristics and distribution patterns. The two main forms of vitiligo are non-segmental vitiligo (NSV), and segmental vitiligo (SV). NSV is the predominant form, characterized by symmetrical skin patches, usually on the extensor surfaces — such as the posterior aspect of the elbow — and the flexural zones, predisposed to mechanical trauma. These lesions tend to evolve over time [2]. In contrast, SV has unilateral or band-shaped lesions that often stabilize early. Distinguishing between these forms is essential for prognosis and treatment guidance. Other variants include mixed vitiligo, where both NSV and SV coexist, and atypical forms such as focal, punctate, minor, and follicular vitiligo [3].

Unmet Need

An unmet need refers in general to a need which is not adequately satisfied by the existing therapeutic alternatives. The terms “need” and “unmet”, although linked one with the other (satisfying a need decreases the entity of the need itself), can be separated for a better understanding of the dimension of the unmet need [4].

The term ‘need’ refers to the severity of the disease. The severity of the disease depends on the perspective adopted in the assessment. From a clinical viewpoint, severity depends on mortality (and life expectancy) and health-related quality of life. Enlarging the perspective from a clinical to a societal viewpoint, domains such as the societal impact of the disease, including its impact on patients’ productivity losses and care-givers burden, and acceptability to patients of existing treatments, should be considered. On the one hand, mortality and health-related quality of life are for sure more important than treatment acceptability. On the other side the latter may have an impact on adherence, effectiveness of treatment and, ultimately, on health. It has been suggested that severity depends on prevalence too. However, prevalence is rarely considered when the level of unmet need is appraised [5].

The term ‘unmet’ could refer to the (i) total absence of alternative treatments or (ii) their presence, but with limited therapeutic impact, or (iii) their availability with a certain therapeutic impact but a critical safety profile and/or low acceptability (barriers to access, critical route of administration). Alternative treatments could include only medicines approved and reimbursed for the same indication, or drugs used off-label on the grounds of less robust clinical evidence [4].

It is thus clear that the dimension of the unmet need depends on the perspective used and inclusiveness of alternatives. The broader is the perspective and the narrower is the definition of ‘validity’ of therapeutic alternatives (an alternative is valid if it has a therapeutic effect, a good safety profile and is acceptable to patients), the higher is the unmet need.

In this perspective, vitiligo is a very interesting case-study. The disease has not an impact on mortality. Guidelines highlight the psychosocial distress due to vitiligo, and the importance of providing psychological support if needed. The social impact of the disease could go beyond the psychosocial distress, leading to stigmatization or discrimination, and a decline in self-esteem [3,6]. A recent systematic review of the literature showed that more than half of patients with vitiligo present depression, major depressive disorder, generalized anxiety disorder, social phobia, feelings of stigmatization, adjustment disorders, sleep disorders, distress, emotional impairment, relational difficulties and cognitive impairment [7]. Compared to the general population, a patient with vitiligo is 5 times more likely to develop depression [8]. Approximately 90% of vitiligo patients suffer from light stigma (24% experienced nasty comments) [9]. 93.2% of adolescents are regularly victims of it (44.6% of nasty comments) and for 21.7% this leads to bullying [10]. A systematic review of observational and interventional studies on humanistic burden of vitiligo was recently published. The review highlighted that a majority of studies based on dermatological-specific or vitiligo-specific instruments revealed moderate to severe effects of vitiligo on the quality of life of patients, families and caregivers [11]. Notwithstanding health-related quality of life for vitiligo is still under-reported and neither specific nor generic health-related quality of life endpoints have been included into the pivotal studies of ruxolitinib, the first medicine approved for vitiligo [12].

Apart from ruxolitinib, there are no approved treatments for vitiligo and medicines used for vitiligo are only partially reimbursed and have important limitations. Topical corticosteroids are reimbursed in Italy for vitiligo through Nota 88 [13] but they have a variable impact on repigmentation; more importantly, they are not suitable for prolonged use due to side effects and should not be used on areas that highly absorb the product. In detail, Nota 88 mentions that 4-6 month courses may be effective in lesions of recent onset and limited extent. Moreover, a regimen whereby the application is stopped for one week every three weeks is proposed to limit potential side effects. However, it should be underscored that these instructions are based on the results of a metaanalysis published in 1998 [14]. Topical calcineurin inhibitors are not reimbursed by the Italian National Health Service and their costs may limit their use over time for...
management [6]. Phototherapy is recommended in patients with vitiligo that do not respond or respond only partially to topical treatments or in those that have extensive or progressive involvement. However, more sessions are necessary to observe an improvement in the disease and the treatment must be continued for several months with 2-3 sessions per week. In Italy the reimbursement of phototherapy is limited to a maximum of six sessions per prescription. Coverage of extra sessions is decided by on a regional base.

It is clear that if a narrow perspective is used - vitiligo is not severe since it has not an impact on mortality and the effects on health-related quality of life are still questionable; alternative treatments are available - the unmet need is not important. If we adopt, on the contrary, a broader perspective - vitiligo has an important impact on the quality of life of patients, relatives and caregivers; alternative treatments are not approved for vitiligo, have critical safety profile and are partially reimbursed by third payers – the unmet need would be much higher.

Managing Patients with Vitiligo

Managing patients with vitiligo requires a meticulous collection of a comprehensive clinical history. Key documentation should include the classification of the lesions, disease extent, skin phototype, age at disease onset, and any potential triggering events. A critical evaluation to ascertain the stability or rapid progression of the disease is essential, as this directly influences the choice of therapeutic modalities. Utilizing medical photography (digital imaging) taken at the onset of treatment and at regular intervals of approximately 3–6 months can assist in both monitoring disease progression and the response to treatment [3,6,15]. A Wood’s lamp examination can represent a supporting tool in confirming both the diagnosis and the extent of the disease in individuals with fair skin. Conversely, histopathologic examination is only occasionally required for diagnostic confirmation [16]. The psychosocial implications, especially the impact on the patient’s quality of life and the psychological distress due to vitiligo, require a thorough assessment. Notably, individuals with vitiligo often face stigmatization, discrimination, and a decline in self-esteem, highlighting the importance of rigorously tracking the psychosocial burden of the disease [6]. Comprehensive assessment tools like the Patient Health Questionnaire-4 [17], Patient Health Questionnaire-9 [18], Generalized Anxiety Disorder [19], and Dermatology Life Quality Index [20] can be used. For a more targeted approach, the Vitiligo Impact Patient Scale [21] and the vitiligo-specific quality-of-life tool [22] are recommended. An additional consideration is the established link between vitiligo and several autoimmune diseases, such as thyroid disorders, pernicious anemia, and Addison’s disease [23]. The likelihood of vitiligo patients developing autoimmune thyroid disease is significantly increased, with a reported 2 to 5-fold rise compared to those without the condition. Moreover, the risk of elevated thyroid antibodies in vitiligo patients is over fivefold higher than in individuals without the disease [24]. Given these observations, it is crucial to evaluate both personal and family histories for thyroid dysfunction and other autoimmune conditions. Consequently, it has been advised to consistently screen for antithyroid antibodies and assess thyroid function, including pediatric patients [6]. These evaluations can identify individuals at an increased risk for developing autoimmune thyroid disorders, allowing for earlier intervention and potentially mitigating further complications.

Management of NSV

Three management guidelines are currently available dealing with the treatment of NSV, i.e., the 2021 edition of the British Association of Dermatologists guidelines [6], the 2022 S1 German guidelines3 and the 2012 European Dermatology Forum consensus [15], whose update has recently been published [25,26].

The 2012 European Dermatology Forum consensus [15] distinguishes between limited (< 2–3% of body surface area) and more extensive NSV, with avoidance of triggering/aggravating factors and camouflage being recommended in both. For limited extrafacial NSV, once daily potent topical corticosteroids (TCS) are advised for a period no longer than 3 months, either continuous or intermittent. For the treatment of limited NSV involving the head and neck region, twice daily topical calcineurin inhibitors (TCI) are recommended as a second line in limited disease, with surgical techniques representing a third line in case of cosmetically unsatisfactory repigmentation on visible areas (preferably in patients with a negative Koebner phenomenon). For generalized NSV, nbUVB therapy for a maximum of 1-2 years is indicated as a first line, with oral Psoralen plus Ultraviolet A therapy (PUVA) still being listed as a second line. nbUVB discontinuation is advised in cases failing to respond within 3 months. According to the 2012 consensus [15], phototherapy may be combined with potent TCS and TCI. For rapidly progressing disease, weekend oral minipulse therapy with dexamethasone for 3-6 months is advised, starting with 2.5 mg daily. The consensus does not specify whether to combine the oral minipulse with phototherapy. Grafiting in nonresponding areas - especially with high cosmetic impact - is suggested as a third line in patients with stable disease, no repigmentation, and a negative Koebner phenomenon. The consensus also covers combinations between different treatment modalities. For example, phototherapy is advised
for 3 or 4 weeks after surgical procedures to enhance repigmentation. Depigmentation techniques (hydroquinone monobenzyl ether or 4-methoxyphenol alone or associated with Q-switched ruby laser) are listed as a fourth line in nonresponsive widespread (>50%) or highly visible recalcitrant facial/hands vitiligo with a positive Koebner phenomenon.

Together with psychological referral, camouflage options, including self-tanning agents, highly pigmented cover creams, and dermal pigmentation/cosmetic tattoos (especially in black people, for depigmented nipples and lips) are also discussed [15].

The update of the EDF/EADV guidelines [25,26] emphasizes a shared decision-making process with three possible treatment goals, i.e., stabilization, repigmentation, and depigmentation.

In NSV that has been active in the previous 6 months, topical treatments with intermittent, prolonged potent once daily TCS and/or twice daily TCI, as well as phototherapy (targeted if needed), are recommended for both stabilization and repigmentation, with optional systemic treatment for rapidly progressive disease (for a maximum of 6 months). When effective, prolonged treatment (e.g., up to 12 months or more) with TCI can be proposed. For NSV that has been stable in the previous 6 months, either clinical follow-up or maintenance treatment with TCS/TCI at least twice a week for 6 months is advised for stabilization. The latter represents a novelty compared with the 2012 version. To pursue repigmentation in stable NSV, important temporal cut-offs are introduced, so that TCS/TCI and phototherapy (targeted if needed) are recommended for cases with stable disease in the previous 6 months, whereas surgical techniques are recommended as an option only for cases that had been stable for at least 12 months and were resistant to treatment [25,26].

The 2021 edition of the British Association of Dermatologists guidelines [5] for the management of people with vitiligo recommends three lines of treatment, irrespective of non-segmental or segmental type of vitiligo, in addition to UV protection, camouflage, psychotherapy, and self-help groups. Specifically, potent or very potent TCS once daily are offered as a first line, avoiding the periorificial area. Tacrolimus 0.1% twice daily is offered as an alternative for facial involvement or under occlusion on photoexposed areas for non-facial vitiligo. Intermittent regimens with potent or very potent TCS with or without TCI are advised for areas with thinner skin. The effectiveness of this first-line, topical approach is periodically reassessed every 3–6 months. As a second line, nbUVB with or without potent or very potent TCS or TCI is offered. However, it is underscored that nbUVB is recommended as a first line in case of extensive or progressive disease. No details are provided concerning nbUVB duration. Systemic corticosteroids (CS) are offered only in rapidly progressive disease, in combination with nbUVB.

A specific regimen is recommended consisting of oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg per month for a further 3 months. As third-line options, excimer laser or light plus TCI is advised for localized disease while CO2 laser (once a month for 5 months) in combination with 5-fluorouracil (once daily for 7 days per month for 5 months) is advised exclusively in adults with NSV on the hands and feet where other treatments have proved ineffective. Surgical treatment, e.g., cellular grafting, is reserved for stable vitiligo unresponsive to other treatments in case of subjective distress, irrespective of non-segmental or segmental type. Finally, depigmentation therapies are advised in people with extensive vitiligo on visible sites, in case of subjective distress [25,26].

The recently published S1 German guidelines [3] recommend a combination of supportive care (UV protection, dermatocosmetics, camouflage, psychotherapy, self-help groups) as well as a series of treatments including TCS/TCI, systemic CS, and phototherapy according to the extent of the involvement. In greater detail, for NSV affecting less than 3% of BSA, potent TCS and/or TCI or targeted light therapy are recommended, either alone or in combination. Intermittent regimens are mentioned as a possibility, but no clear recommendation is given. In case of successful repigmentation, proactive therapy with TCI twice a week as maintenance is recommended.

Concerning light-based therapies, the German guidelines advocate in favor of 308-nm excimer laser or lamp as the first choice in NSV or SV of limited extent, due to the lower dose as compared with nbUVB to achieve the same result.

For NSV involving more than 3% of BSA, the therapeutic algorithm differentiates chronic from acute, rapid, and progressive forms. The former are treated by means of nbUVB and potent TCS and/or TCI, while the latter may also benefit from a course with systemic CS. Systemic CS should not be administered as monotherapy and consists of an oral mini-pulse therapy of 3–6 months with betamethasone, dexamethasone (e.g., for both, 5 mg on two consecutive days per week with a potential increase to 7.5 mg in case of non-response), prednisone or methylprednisolone. Periodic reassessment of the effectiveness of nbUVB is recommended every 3 months, with nbUVB discontinuation after 6 months in case of non-response. Overall, no more than 12–24 months should be administered.

Surgical options are recommended in case of unresponsive and stable disease, with no specific indication of the optimal technique. Depigmentation is recommended only in extremely rare cases of subtotal vitiligo and after exploitation of all options [3].

After the Food and Drug Administration (FDA) and European Medicine Agency (EMA) approval, respectively in
July 2022 and February 2023, topical ruxolitinib (TR) has opened up options for treatment of NSV. Based on the results of the phase III registration trial of the twice-daily application, especially for lesions on the face (more than 75% improvement in facial VASI at 24 weeks compared to controls with limited side effects), TR seems to have the best use in localized NSV no longer responding to conventional topical agents or to reduce risk of greater adverse effects. The association of TR with phototherapy has been investigated with good results but larger studies are needed to confirm these findings [12,27].

Management of SV

The same four guidelines also provide guidance for the management of SV [3,6,15,25,26].

As SV progresses but also reaches stabilization rapidly, a slightly different approach is required.

Like in limited NSV, the 2012 European Dermatology Forum consensus [4] recommends: avoidance of triggering factors and camouflage; once daily potent TCS for a period no longer than 3 months, either continuous or intermittent; and twice daily TCI for the head and neck region, initially for 6 months and then if effective for longer. While oral minipulse therapy with systemic CS is listed as an option for rapidly progressing disease, irrespective of non-segmental or segmental type, it is not reported in the suggested algorithm for the management of SV. Localized nbUVB therapy and, especially, excimer monochromatic lamp or laser are listed as the second line in case of progression under topical treatment. If stabilization without repigmentation is achieved, surgical techniques are advised as an option in patients with a negative Koebner phenomenon. For those with a positive Koebner phenomenon, camouflage is recommended. Depigmentation is not explicitly listed as an option for SV but, as for NSV, it may be considered in nonresponding widespread (> 50%) or highly visible recalcitrant facial / hands vitiligo with a positive Koebner phenomenon [15].

The recently published update of the EDF/EADV guidelines [25,26] maintains the two possible treatment goals, stabilization and repigmentation, but different temporal cut-offs are adopted relative to NSV. In SV that has been active in the previous 12 months, topical treatments with intermittent, prolonged TCS and/or twice daily TCIs as well as phototherapy (targeted if needed) are recommended for both stabilization and repigmentation. Maintenance with TCS and or TCI is not listed/needed in SV. While systemic CS are listed as an option for rapidly progressing disease, irrespective of non-segmental or segmental type, they are not reported in the suggested algorithm for the management of SV. For SV that has been stable in the previous 12 months, only clinical follow-up is advised if the goal of stabilization is pursued. Conversely, for stable cases that have proven resistant to topical treatment and/or phototherapy and in which the goal of repigmentation is pursued, surgical techniques are advised [25,26].

As stated, the 2021 British Association of Dermatologists guidelines propose a similar outline for the management of NSV and SV. In detail, potent or very potent TCS once daily are offered as a first line, avoiding the periorcular area. Tacrolimus 0.1% twice daily is offered as an alternative for facial involvement or under occlusion on photoexposed areas for non-facial vitiligo. Intermittent regimens with potent or very potent TCS with or without TCI are advised for areas with thinner skin. As a second line, nbUVB with or without potent or very potent TCS or TCI is offered. Systemic CS are offered in rapidly progressive disease in combination with nbUVB. The same regimen is recommended consisting of oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg per month for a further 3 months. Excimer laser or light plus TCI are listed as third-line options, mainly due to limited availability. Surgical treatment, e.g., cellular grafting, is reserved for stable vitiligo unresponsive to other treatments, in case of subjective distress. According to the guidelines, depigmentation is to be considered only in case of extensive disease, irrespective of non-segmental or segmental type [6].

The S1 German guidelines [3] distinguish between acute and chronic forms of SV. For chronic SV, potent TCS and/or TCI or targeted light therapy are recommended, either alone or, preferably, in combination. For acute SV, a regimen consisting of systemic CS (see above for details) plus potent TCS and/or TCI plus targeted light therapy is advised. Finally, in case of stable and unresponsive disease, surgical therapy is recommended. Depigmentation is recommended only in extremely rare cases of subtotal vitiligo after the exploitation of all options and is not specifically mentioned for SV. Similarly to NSV, supportive care (UV protection, dermatocosmetics, camouflage, psychotherapy, self-help groups) is also recommended [3].

Conclusions

As new therapeutic options are being approved for vitiligo and many more are currently under investigations, patients still experience a substantial unmet need in terms of psychological distress and lack of effective and available therapeutic approaches. The review examined the disconnect between the current prescription/reimbursement scenario in Italy and recommendations from the most recent guidelines. Negotiation of reimbursement of new and selective treatment options will soon define their use in Italy, with important implications for the management of this often under-treated but potentially dramatic dermatological disease.
References
