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Vitiligo: Unmet Need, Management and Treatment Guidelines

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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-scaly, 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 psychological 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 metanalysis 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

maintenance [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 advised, initially for 6 months and then if effective for longer. Localized narrowband Ultraviolet B (nbUVB) therapy and, especially, excimer monochromatic lamp or laser 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. Grafting 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 non-responding 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 periocular 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 formers 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 registrational 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 periocular 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.

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