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Viewpoint

Beyond vitiligo guidelines: combined stratified/personalized approaches for the vitiligo patient

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Abstract: 'Vitiligo' is a word that bears endless possibilities and no promises. Each vitiligo patient has a different story that demands a different therapeutic approach. Even though great efforts have been made to evaluate, study, compare and document the different therapeutic modalities available for vitiligo, clearly handling their modes of actions as well as their side effects and establishing clear stratified guidelines, numerous dilemmas are frequently met on practical grounds. 'Stabilize', 'repigment', 'depigment' or 'camouflage'? 'for whom and how do we achieve the best results' ? 'Separately or in combination ? – questions that need to be answered and decisions need to be taken in the appropriate timing and altered when the necessity arises. In the current viewpoint, we have utilized the available knowledge and exploited years of experience in an attempt to go beyond the guidelines to set the rationale for an optimal and personalized therapy, within the framework of a stratified approach.

Key words: guidelines – repigmentation – stabilization – treatment – vitiligo

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Introduction

Several treatment guidelines have been recently published and great efforts have been made to evaluate the response of the different therapeutic modalities available whether separately or in combination (1–10).

The major measurable outcome in vitiligo for physicians and patients is repigmentation. 'Stabilizing your patient', a very important general recommendation because it means 'no more pigment cell losses', is however sometimes overlooked. The literature is more oriented towards regaining pigmentation as an independent goal. Indeed, the proper definition of disease stabilization and its assessment through clinical or non-clinical markers is not well covered in guidelines, as recently mentioned at an international consensus conference (11). Accumulating evidence indicates that inflammation occurring latently in vitiligo challenges our attempts to achieve repigmentation. This subclinical and abbreviated inflammation, when reactivated in an explosive manner (Fig. 1), has a noxious effect on melanocytes that results in bouts of disease activity and failure of treatment attempts. Even if ideal disease stabilization could be achieved, the best strategy for repigmentation still needs to be well designed to achieve the desired 100% repigmentation. In current practice however, this objective is rarely, if ever, reached. Thus, the initial strategy balancing 'repigmentation' versus 'depigmentation' needs to be carefully planned.

The aim of this review is to set the rationale for an optimal and personalized therapy, within the framework of a stratified approach for vitiligo (8); thereby, a scenario of the sequence of events that occur upon repigmentation is first highlighted.

Lessons from repigmentation patterns: perifollicular, marginal and diffuse

In spontaneous or medically induced repigmentation, melanocytes may arise from various sources, as evidenced by the three observable patterns, namely perifollicular, marginal and diffuse (7). Thereby, notwithstanding gaps in our current understanding of vitiligo pathophysiology, but instead depending on the real solid end result which is the absence of functioning melanocytes from such available sources to achieve repigmentation.

The hair follicle unit

The mechanism of perifollicular repigmentation has been researched extensively, and it has been established that most melanocytes migrating to the epidermis originate from the hair follicle unit (12). Melanocyte stem cells have been identified in the lower permanent portion of transgenic mice hair follicles, which become activated at the early anagen phases (13). It is assumed that they are maintained in a specific environment (the niche) in the lower part of the bulge (14). Immunohistological and histomorphometric studies of normal human scalp hairs have shown that the bulge region is a site of relative immune privilege, protecting the follicular epithelial stem cell reservoir from auto-aggressive immune attacks (15).

The edge

In the border of vitiligo patches, melanocytes are often prominent and demonstrate long dendrites filled with melanin (16). These melanocytes are expected to be able to migrate and thus substitute for pigment cell losses (17). Unfortunately, the usual distance of this migration in vitiligo is small, that is, 2–3 mm (18). This poorly explained limited capability of horizontal migration of melanocytes is still a major challenge for appropriate regenerative therapy.

Other possible sources

The diffuse repigmentation pattern that is frequently observed (7) has raised the question of a possible additional reservoir. Reactivation of DOPA-negative melanocytes in the centre of lesions might be responsible for this type of repigmentation (19). The presence

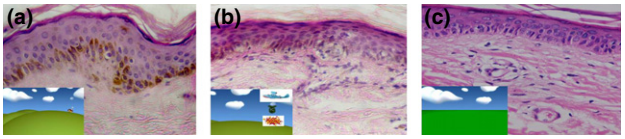


Figure 1. (a) Normal skin showing melanocytes. (b) Lymphocytes attacking the melanocytes before their disappearance . (c) The disappearance of the inflammatory infiltrate after completing its short-timed mission of melanocyte destruction.

of such melanocytes has been supported by some authors (7,19–21) and denied by others (17,22,23), but this discrepancy may relate to a lesional stage.

Epidermal stem cells lie in niches in the interfollicular epidermis, sebaceous gland and bulge regions of hair follicles. These epidermal stem cells renew the epidermis, the sebaceous glands and hair follicles after mature cells die. Dermal stem cells lie in the hair papillae, around pericytes and elsewhere among other dermal cells. These form pericytes, myoblasts, fibroblasts, chondrocytes and other specialized dermal cells (24). Besides being in a privileged site, stem cells go undetected because they do not (yet) express common target antigens or MHC. The existence of similar melanocyte stem cells that may act as an undetectable reservoir cannot be excluded. Recently, studies have suggested that extrafollicular dermal melanocyte stem cells persist after birth in the superficial peripheral nerve sheaths and may give rise to migratory melanocyte precursors (25). These immature melanocyte precursors and the DOPA-negative melanocytes may be considered as other possible sources of repigmentation.

Because of the speculative and contradictory data on these sources in human skin, we will concentrate on the first two sources. Accordingly, we will consider two types of migration, that is, 'vertical' towards the basal cell layer and 'horizontal' across the vitiligo border, resulting in perifollicular and marginal repigmentation patterns, respectively.

Factors affecting the density of functioning melanocytes

Anatomical factors

According to the site of the vitiligo lesions, three patterns of repigmentation could be predicted: (A) areas devoid of hair, for example, mucous membranes, palms and soles: the horizontally migrating melanocytes from the edge will in this case be the only source of repigmentation (Fig. 2a); (B) areas with scanty hair, for example, flexor surface of the wrist and the dorsum of the foot: repigmentation would be expected to occur similar to type (A) together with little perifollicular pigmentation, resulting in a negligible therapeutic effect (Fig. 2b); (C) areas with numerous pigmented hair, for example, face and trunk: despite the fact that the two main origins for melanocyte migration are available, the marginal mode has a negligible therapeutic outcome compared to the multiple perifollicular coalescing pigmentary macules, resulting from the vertical migration (Fig. 2c). Still, on considering Fig. 2c, the role of diffuse repigmentation arising from putative interfollicular precursors should be considered, as the full recovery of a lesion cannot logically be attributed to both those routes alone due to the usual limited migratory capacity of the melanocytes (2–3 mm) (18). An intriguing point is that on revising the literature and from our experience, the diffuse pattern of repigmentation is not mentioned or met in glabrous areas, which might point to a possible relation between diffuse pigment spread and density of hair follicles. In summary, the origin of diffuse repigmentation in areas of vitiligo with profuse black hair is still unclear.

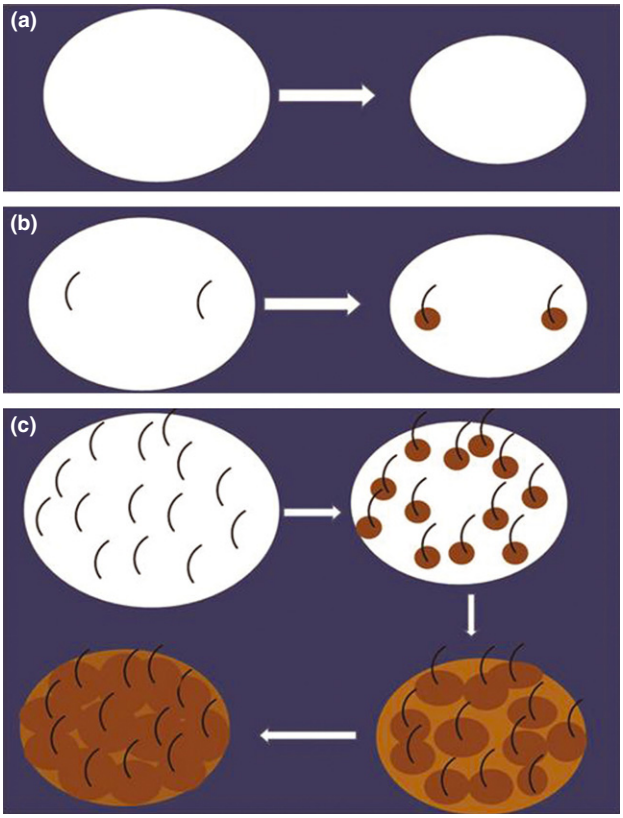


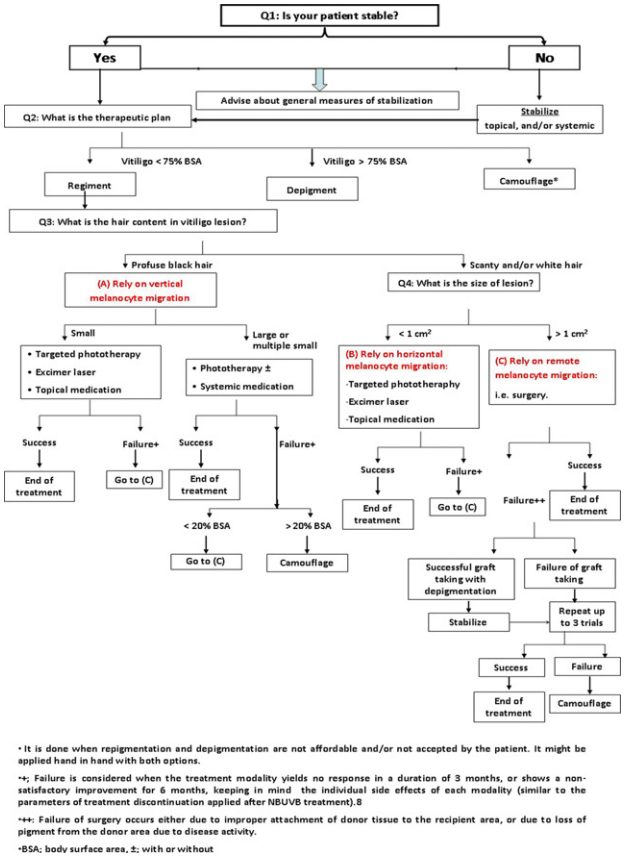
Figure 2. Patterns of repigmentation of vitiligo lesions: (a) In areas with no hair, marginal repigmentation from the nearby melanocytes in the normal skin. (b) In areas with scanty hair, similar to (a) plus few perifollicular pigmentation with negligible clinical effect. (c) In areas with abundant pigmented hair, both marginal and follicular modes apply; however, the follicular pigmentation has the upper hand as its coalescence leads to complete repigmentation of the lesion.

Pathological factors

As we assume that leukotrichia is related to melanocyte reservoir exhaustion, repigmentation using medical therapies in vitiligo with leukotrichia is very unlikely (26). This has been confirmed by an immunohistochemical study that demonstrated the absence of the amelanotic melanocytes in all white hairs in vitiligo patches (20). The presence of pigmented hairs in vitiligo is a good prognostic sign suggesting an intact melanocyte reservoir (27), but it is not a guarantee for the efficient mobilization of hair follicle melanocytes. The probability of repigmentation originating from this source is inversely proportional to the duration of the patch (20), a suggestion supported by the clinical observation of many authors (28,29).

Practical deductions for a combined stratified/personalized approach

Based on the factors that influence the density of functional melanocytes available for both 'vertical' and 'horizontal' migration, one should be able, after careful assessment, to make a prognosis for



• It is done when repigmentation and depigmentation are not affordable and/or not accepted by the patient. It might be applied hand in hand with both options.

•+; Failure is considered when the treatment modality yields no response in a duration of 3 months, or shows a non-satisfactory improvement for 6 months, keeping in mind the individual side effects of each modality (similar to the parameters of treatment discontinuation applied after NBUVB treatment).8

•++: Failure of surgery occurs either due to improper attachment of donor tissue to the recipient area, or due to loss of pigment from the donor area due to disease activity.

•BSA; body surface area, ±; with or without

Figure 3. Flow chart showing the stratified approach to management of vitiligo.

repigmentation and to plan a treatment. The decision whether to 'repigment', 'depigment' or 'camouflage' the lesions is essential to the plan. Camouflaging may target either the depigmented lesions or the islands of normally appearing skin on a background of vitiliginous skin.

The therapeutic decision should be taken based more on these premises and personal experience than on current written guidelines/recommendations which provide little guidance for a personalized approach. Treatment should never be commenced without in-depth discussion with the patient to meet realistic expectations. A flow chart showing the stratified approach to management of vitiligo is presented in Fig. 3, bearing in mind that one could shift from one successful therapeutic regimen to another to reduce the anticipated side effects.

Furthermore, a change of strategy should be possible throughout the course of treatment and follow-up. This may be due to a change in the disease itself or in the patient's concepts and/or demands. Failure to obtain repigmentation may necessitate a change of policy towards depigmentation or camouflage. Furthermore, a patient refusing camouflage during the repigmentation protocol may change his/her mind due to social insults; thus, a combined policy including 'repigmentation' and 'camouflaging' should be adopted (Fig. S1).

In summary, after patient's approval, three directions have to be considered: (i) keeping the normal skin colour and enhancing repigmentation, (ii) keeping the depigmented colour and extending depigmentation and (iii) camouflaging the undesirable colour alone or in combination with one of the above-mentioned two directions.

The personalized options: repigmentation/depigmentation/camouflage/combined

Repigmentation

If repigmentation is the desired goal, controlling disease progression needs to be addressed as the first line of intervention, as a patient who is achieving some repigmentation but continues to have fresh lesions elsewhere, or expansion of his/her already existing lesions will never be satisfied or termed as 'cured' (30).

For repigmentation to be achieved, as mentioned earlier, vertical and horizontal melanocyte migrations need to be optimized from local sources. Most therapeutic options work on both aspects, and different combinations between topical, systemic and light-based therapies seem overall synergistic in that sense. The choice of surgery, which depends upon 'remote' melanocytes, is the third possible option. Despite the fact that segmental vitiligo has a different story than non-segmental vitiligo (31), the therapeutic plan proposed in the current viewpoint is applicable for segmental vitiligo, but with the urgency of early commencement of treatment. This is to avoid the entry in the 'early' leucotrichia phase that is one of the major clinical characteristics of segmental vitiligo patients (32), which would deem the loss of the source of the vertical melanocyte migration.

Relying on vertical melanocyte migration

The presence of numerous pigmented hairs would ultimately lead to them being a reliable source of melanocytes for repigmentation. The expected outcome is good especially in cases of short duration. Although the size of the lesion would not affect the choice of this source of melanocytes, it is expected to affect the choice of the technique used, for example total body NBUVB for large body surface area (Fig. S1a) versus targeted NBUVB (Fig. S2) or Excimer lamps or laser for small-sized lesions.

Relying on horizontal melanocyte migration

The presence of vitiliginous lesion, which either is devoid of hairs, or contains white or scanty pigmented hairs, excludes the dependence on hair follicles, and thus, the dependence will be on the horizontal migration. In this case, the size of the lesion would be the most important factor. Based on personal experience, if it is more than 1 cm^2, we cannot depend on the edge because of the limited horizontal melanocyte migration capacity.

Combination between different topical, systemic and light-based therapies could logically boost the therapeutic response, for example, combination between erbium-YAG-laser ablation and application of 5-fluorouracil on ablated skin (33,34) has been shown to aid in this type of pigmentation in small areas. However, unresponsiveness would suggest moving to the third option.

Relying on remote melanocytes

In lesions with minimum therapeutic impact for either source of melanocytes, the dependence on remote melanocytes through surgical intervention seems currently the only logical option, given that disease stabilization is achieved in parallel by basic therapy.

The size of lesions is important because if too large, the shortage of a donor area that would be able to cover such lesion, together with the necessity of multiple, costly and long operations, argues against this choice. Nevertheless, the surgical option (usually followed by phototherapy) can be taken as the only protocol

in certain situations, for example, in lesions on the dorsa of feet greater than can be covered by the expected migration from the edge (Fig. S3). In other instances, similar lesions can be present accompanying medically treatable lesions. In this case, it is more advisable to start with the medical treatment and then continue with surgery. The plan should be clear to the patient from the start, and usually when the patient finds that the face and the trunk responded as he/she was informed beforehand, while the dorsum of the foot did not, his confidence and acceptance of the operation will increase. Furthermore, even if the surgical option was not a choice made during the first visit, it should be kept in mind for areas which do not follow our expectations and fail to repigment, an incident that could be met in this 'unpredictable disease' (Fig. S4).

Depigmentation

Depigmentation of the remaining islands of skin colour should be chosen if the previously mentioned options are not adequate. It must be reserved for cases where the vitiligo lesions cover most of the body surface, or most of a given location not amenable to other options; however, the exact percentage is much debated (4), and rather part of a personalized management plan.

Depigmentation can be achieved through chemical methods (monobenzyl ether of hydroquinone 20 %(35) (Fig. S5) and monomethyl ether of hydroquinone (36)), or physical methods (Q-switched Alexandrite laser (755 nm)(37), Q-switched Ruby laser (694 nm) (38) and Cryotherapy (39)). In all cases, patients must be extensively informed that most approaches lead to irreversible depigmentation.

The camouflage option

Camouflaging a vitiligo lesion could be considered when pigmentation and depigmentation are not realistic, or it may be applied hand in hand with both options considering the impact of the disease on the patient's quality of life (Fig. S1b).

Camouflage in vitiligo can be broadly classified into temporary and permanent. Temporary camouflage includes liquid dyes, indigenous products, foundation-based cosmetic camouflage and self-tanning products (40). Patients should be helped in selecting and using a camouflage preparation that best suits their needs (41); thus, the concept of 'camouflage therapists' has gained much ground in some countries (42). The easy 'reversibility' of those products definitely gives them an edge over the coming group.

Permanent camouflage is achieved mainly by micropigmentation/medical tattooing. Nevertheless, it should be noted that such permanent techniques are frequently associated with 'stubborn' adverse events including koebnerization, allergic reactions, imperfect colour matching (2) and colour change of the tattoo pigment over time (Fig. S6a) which could even happen after a test session (Fig. S6b). The negative impact such drawbacks have on the patient's psyche sometimes exceeds the disease itself and makes this technique questionable. In our experience, we believe that it is risky to use permanent foreign pigment with unpredictable outcome in a disease with an unpredictable course.

Conclusion

The current practical stratified/personalized approach described in this paper offers a guide for dealing with vitiligo patients beyond the set guidelines within a stratified approach. It helps to visualize each patient as a separate case and enables one to tailor the suitable personalized treatment plan accordingly. We tried to tackle the different clinical dilemmas met in our daily clinical practice on dealing with a vitiligo patient and in the meantime acknowledge the current limitations that hinder our therapeutic achievements. This proposed approach will be challenged and improved by the ongoing international efforts to decipher the pathophysiology of this disease and to make vitiligo a 'druggable' one.

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Conflict of interest

The authors have declared no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Vitiligo stabilization: When and how?

Table 1. Stabilizing measures that could be adopted in cases of vitiligo.

Table 2. Suggestions for future research to improve the therapeutic aspects of vitiligo.

Figure S1. Combined camouflaging/repigmentation policy; (a) responding large lesions on the limbs were treated traditional NB-UVB phototherapy, while periungual lesions extending to involve the whole fingers did not respond to the NB-UVB phototherapy in the same patient and were thus treated by camouflaging (b).

Figure S2. Focal vitiligo lesions treated by targeted NB-UVB.

Figure S3. Lesions on the feet with size beyond the capacity to repigment by the melanocyte migration from the borders were treated with non-cultured melanocyte suspension.

Figure S4. Unpredictable response to vitiligo treatment: (a) An unexplained remaining spot of vitiligo after successful treatment of other parts of the body with NB-UVB for 10 months, (b) marked improvement after punch grafting.

Figure S5. Depigmentation of the remaining normal skin colour in cases of universal vitiligo using MBEH (courtesy of Dr. Ahmed El Eissa).

Figure S6. Tattoo in vitiligo lesions (a) over the back which changed by time to unsightly bluish coloration and (b) after a test session over the knees resulting in two shades of color (arrows) which were unaccepted by the patient.