Dermatology Practical & Conceptual

Vitiligo: Current Therapies and Future Treatments

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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 acneiform 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 povorcitinib (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 under way [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 HSP70i 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

1. Geel N, Speeckaert R, Taïeb A, *et al.* Worldwide expert recommendations for the diagnosis and management of vitiligo: Position statement from the International Vitiligo Task Force Part 1: towards a new management algorithm. *J Eur Acad Dermatol Venereol* 2023.
2. Seneschal J, Speeckaert R, Taïeb A, *et al.* Worldwide expert recommendations for the diagnosis and management of vitiligo: Position statement from the international Vitiligo Task Force—Part 2: Specific treatment recommendations. *J Eur Acad Dermatol Venereol* 2023.
3. Zhang L, Chen S, Kang Y, *et al.* Association of Clinical Markers With Disease Progression in Patients With Vitiligo From China. *Jama Dermatol* 2020;**156**.
4. Sosa JJ, Currimbhoy SD, Ukoha U, *et al.* Confetti-like depigmentation: A potential sign of rapidly progressing vitiligo. *J Am Acad Dermatol* 2015;**73**:272–5.

5. Geel N van, Speeckaert R, Wolf JD, *et al.* Clinical significance of Koebner phenomenon in vitiligo. *Brit J Dermatol* 2012;**167**:1017–24.
6. Geel N van, Grine L, Wispelaere PD, Mertens D, Prinsen CAC, Speeckaert R. Clinical visible signs of disease activity in vitiligo: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2019;**33**:1667–75doi:10.1111/jdv.15604.
7. Geel N van, Passeron T, Wolkerstorfer A, Speeckaert R, Ezzedine K. Reliability and validity of the Vitiligo Signs of Activity Score (VSAS). *Brit J Dermatol* 2020.
8. Passeron T. Medical and Maintenance Treatments for Vitiligo. *Dermatol Clin* 2017;**35**:163–70.
9. Tovar-Garza A, Hinojosa JA, Hynan LS, Pandya AG. Addition of oral minipulse dexamethasone to narrowband ultraviolet B phototherapy and topical steroids helps arrest disease activity in patients with vitiligo. *The British journal of dermatology* 2019;**180**:193–4.
10. Passeron T, Ostovari N, Zakaria W, *et al.* Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Arch Dermatol* 2004;**140**:1065–9.
11. Seneschal J, Duplaine A, Maillard H, *et al.* Efficacy and Safety of Tacrolimus 0.1% for the Treatment of Facial Vitiligo: A Multicenter Randomized, Double-Blinded, Vehicle-Controlled Study. *J Investig Dermatol* 2021;**141**:1728–34.
12. Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Archives of Dermatology* 2003;**139**:581–5.
13. Rosmarin D, Passeron T, Pandya AG, *et al.* Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo. *New Engl J Med* 2022;**387**:1445–55.
14. Esmat SM, El-Mofty M, Rasheed H, *et al.* Efficacy of narrow band UVB with or without OMP in stabilization of vitiligo activity in skin photo-types (III–V): A double-blind, randomized, placebo-controlled, prospective, multicenter study. *Photodermatol Photoimmunol Photomed* 2021.
15. Esmat S, Hegazy RA, Shalaby S, Hu SC-S, Lan C-CE. Phototherapy and Combination Therapies for Vitiligo. *Dermatologic clinics* 2017;**35**:171–92.
16. Esmat S, Mostafa W, Hegazy RA, *et al.* Phototherapy: The vitiligo management pillar. *Clin Dermatol* 2016;**34**:594–602.
17. Mohammad TF, Al-Jamal M, Hamzavi IH, *et al.* The Vitiligo Working Group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo. *Journal of the American Academy of Dermatology* 2017;**76**:879–88.
18. Mohammad TF, Silpa-Archa N, Griffith JL, Lim HW, Hamzavi IH. Home phototherapy in vitiligo. *Photodermatology, Photoimmunology & Photomedicine* 2017;**33**:241–52.
19. Batchelor JM, Millington A, Thomas KS, *et al.* Home-based narrowband UVB, topical corticosteroid or combination for children and adults with vitiligo: HI-Light Vitiligo three-arm RCT. *Heal Technol Assess* 2020;**24**:1–128.
20. Teulings HE, Overkamp M, Ceylan E, *et al.* Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. *British Journal of Dermatology* 2012;**168**:162–71doi:10.1111/bjd.12111.
21. Bae JM, Ju HJ, Lee RW, *et al.* Evaluation for Skin Cancer and Precancer in Patients With Vitiligo Treated With Long-term Narrowband UV-B Phototherapy. *Jama Dermatol* 2020;**156**:529–37.
22. Ju HJ, Han JH, Kim M-S, *et al.* The long-term risk of lymphoma and skin cancer was not increased after topical calcineurin inhibitor use and phototherapy in a cohort of 25,694 patients with vitiligo. *J Am Acad Dermatol* 2021.
23. Mohammad TF, Hamzavi IH. Surgical Therapies for Vitiligo. *Dermatologic clinics* 2017;**35**:193–203.
24. Ju HJ, Bae JM, Lee RW, *et al.* Surgical Interventions for Patients With Vitiligo. *JAMA Dermatol* 2021;**157**:307–16.
25. Nicolaidou E, Antoniou C, Stratigos AJ, Stefanaki C, Katsambas AD. Efficacy, predictors of response, and long-term follow-up in patients with vitiligo treated with narrowband UVB phototherapy. *J Am Acad Dermatol* 2007;**56**:274–8.
26. Cavalié M, Ezzedine K, Fontas E, *et al.* Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo-controlled study. *The Journal of investigative dermatology* 2015;**135**:970–4.
27. Komen L, Zwertbroek L, Burger SJ, Veen JPW, Rie MA, Wolkerstorfer A. Q-switched laser depigmentation in vitiligo, most effective in active disease. *Brit J Dermatol* 2013;**169**:1246–51.
28. MOSHER DB, PARRISH JA, FITZPATRICK TB. Monobenzylether of hydroquinone. *Brit J Dermatol* 1977;**97**:669–79.
29. Ezzedine K, Peeva E, Yamaguchi Y, *et al.* Efficacy and safety of oral ritlecitinib for the treatment of active nonsegmental vitiligo: A randomized phase 2b clinical trial. *J Am Acad Dermatol* 2023;**88**:395–403.
30. Richmond JM, Strassner JP, Zapata L, *et al.* Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci Transl Med* 2018;**10**:eaam7710.
31. Jacquemin C, Rambert J, Guillet S, *et al.* Heat shock protein 70 potentiates interferon alpha production by plasmacytoid dendritic cells: relevance for cutaneous lupus and vitiligo pathogenesis. *The British journal of dermatology* 2017;**177**:1367–75.
32. Mosenson JA, Eby JM, Hernandez C, Poole ICL. A central role for inducible heat-shock protein 70 in autoimmune vitiligo. *Experimental Dermatology* 2013;**22**:566–9.
33. Mosenson JA, Zloza A, Nieland JD, *et al.* Mutant HSP70 Reverses Autoimmune Depigmentation in Vitiligo. *Science translational medicine* 2013;**5**:174ra28-174ra28.
34. Boukhedouni N, Martins C, Darrigade A-S, *et al.* Type-1 cytokines regulate matrix metalloprotease-9 production and E-cadherin disruption to promote melanocyte loss in vitiligo. *Jci Insight* 2020.
35. Bzioueche H, Sjödin KS, West CE, *et al.* Analysis of Matched Skin and Gut Microbiome of Patients with Vitiligo Reveals Deep Skin Dysbiosis: Link with Mitochondrial and Immune Changes. *J Invest Dermatol* 2021;**141**:2280–90.
36. Regazzetti C, Joly F, Marty C, *et al.* Transcriptional Analysis of Vitiligo Skin Reveals the Alteration of WNT Pathway: A Promising Target for Repigmenting Vitiligo Patients. *J Invest Dermatol* 2015;**135**:3105–14.