

Current and emerging treatments for vitiligo



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Learning objectives

After completing this learning activity, participants should be able to choose an optimal approach to management of all patients with vitiligo; list the risks associated with treatment for vitiligo; and discuss emerging treatment options for vitiligo.

Disclosure

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Clinicians should be aware that vitiligo is not merely a cosmetic disease and that there are safe and effective treatments available for vitiligo. It is important to recognize common and uncommon presentations and those with active disease, as well as their implications for clinical management; these were discussed in the first article in this continuing medical education series. Existing treatments include topical and systemic immunosuppressants, phototherapy, and surgical techniques, which together may serve to halt disease progression, stabilize depigmented lesions, and encourage repigmentation. We discuss how to optimize the currently available treatments and highlight emerging treatments that may improve treatment efficacy in the future. (J Am Acad Dermatol 2017;77:17-29.)

Key words: afamelanotide; biologics; corticosteroids; excimer lamp; excimer laser; grafting; leukoderma; methotrexate; narrowband ultraviolet light; phototherapy; pigmentation; tacrolimus; treatment; vitiligo.

MEDICAL TREATMENTS

Key points

- **Potent or ultrapotent topical corticosteroids administered in a cyclical fashion avoids adverse effects**

- **Topical tacrolimus 0.1% should be used twice daily for affected areas on the face and intertriginous areas**
- **Narrowband ultraviolet B light phototherapy appears to be safe and effective when >5-10%**

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body surface area is affected; focused narrowband ultraviolet B light phototherapy, such as hand and foot units or excimer laser, is useful in localized disease

- **Topical tacrolimus 0.1% used twice per week may help prevent relapse after repigmentation is achieved**

Vitiligo is not a “cosmetic disease,”¹ so treatment can and should be offered to patients. The optimal treatment of vitiligo will first depend on the subtype of the disease, percent of body surface area (BSA) involved, effect on quality of life, and the perception of the patient concerning the risk to benefit ratio. For example, in the segmental variant of vitiligo, the disease follows a predictable course, with a phase of rapid spreading and early hair follicle involvement restricted to the affected segment lasting 3 to 24 months. This is usually followed by complete stabilization. The segmental variant is therefore more difficult to treat and requires early medical intervention or a surgical approach late in the disease course. With all types of vitiligo, timing of treatment is an important predictor of success, with early disease responding best.²

In contrast to the segmental variant, most cases of vitiligo follow an unpredictable course, with periods of disease progression and quiescence. Early involvement of the hair follicle is uncommon.³ Spontaneous repigmentation has been described, although this is not the rule. At present, no medical treatment for repigmenting vitiligo has been approved by the US Food and Drug Administration (FDA), and therefore treatments are used off-label. Topical treatments may be applied alone when small areas are involved or when other treatment modalities are not readily available. Phototherapy combined with topical treatment is preferred when >5-10% of the BSA is affected or when focal areas are unresponsive to topical treatments alone.

Topical corticosteroids (level II evidence)

When selecting a topical steroid, the site of the lesion and age of the patient should be considered. Lesions on the body may be treated with ultrapotent or potent corticosteroids; the face, neck, and intertriginous areas and lesions in children should be treated with either midpotency topical corticosteroids or calcineurin inhibitors (see below). Possible regimens include daily or twice daily application in a cyclical fashion with “days off” (eg, 1 week on then 1 week off for 6 months, or application for 5 consecutive days followed by 2 days off).⁴ In practice, these regimens appear to minimize the risk of adverse effects, although evidence-based studies to support this are lacking.

Topical calcineurin inhibitors (level II evidence)

In recently published guidelines, the European Dermatology Forum group proposed twice daily topical calcineurin inhibitors for head and neck lesions as a first-line approach.⁵ This recommendation is based on a combination of its efficacy in these sites and its favorable side effect profile.^{6,7} Warnings have been placed on the long-term use of tacrolimus because of a theoretical long-term risk of cancer, despite its repeatedly demonstrated safety.⁸ Other than exposure to medically administered phototherapy or excimer laser, photoprotection should be encouraged when using topical immunosuppression. When using a cyclical regimen for topical steroids outlined above, calcineurin inhibitors may be used on the “off” days to provide consistent treatment without increasing the risk of adverse events.

Phototherapy

There are 2 main indications for the use of whole-body phototherapy in vitiligo: extensive disease (>5-10% of BSA) and rapidly spreading disease. However, patients with smaller areas of involvement and less activity may also require phototherapy in some instances because of its superior efficacy. With all medical interventions, the physical and psychological impact of the disease should be weighed against the risks of a particular treatment, which typically requires physicians to customize the management strategy for each patient. In general, patients should not apply any topical medications or sunscreen before ultraviolet (UV) light therapy in order to avoid reduced transmission of UV light into the skin. Patients should also be vigilant about sun protection to avoid additive effects of sun exposure when receiving UV light therapy treatment.

Psoralen plus ultraviolet A light phototherapy (level I evidence)

Psoralen plus ultraviolet A light phototherapy (PUVA) was the first phototherapy regimen used in patients with vitiligo. The results were reasonable, but issues with compliance (eg, oculocutaneous protection), side effects (eg, nausea), and an increased risk of skin cancer led to a decline in its use. In a recent Cochrane review, PUVA was deemed inferior to narrowband ultraviolet B light therapy (NB-UVB) in achieving >75% repigmentation in the general population of vitiligo patients.⁶ Therefore, PUVA has been largely replaced by NB-UVB, although PUVA may still induce faster repigmentation.^{9,10} PUVA may be considered in patients with

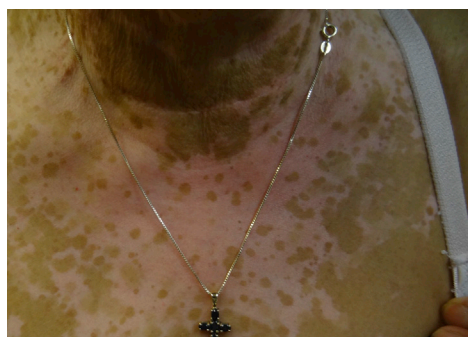


Fig 1. Vitiligo. Carnation pink color of vitiligo in a patient being treated with narrowband ultraviolet B light phototherapy.

darker Fitzpatrick skin phototypes or those with treatment-resistant vitiligo.¹¹⁻¹³

NB-UVB (level I evidence)

In addition to its immunosuppressive effects, NB-UVB induces melanocyte differentiation and melanin production.¹⁴ In the last decade, NB-UVB has become the first-line therapy for extensive, progressive vitiligo because of its superiority to PUVA and its relative paucity of side effects. It can also be used safely in children and those who are pregnant or lactating. When used alone, repigmentation rates ranging from 40% to 100% have been reported, depending on the location of the lesions.¹⁵⁻¹⁹ Patients should be treated with an optimized, aggressive approach, starting at a safe, low dose (ie, 200 mJ) 2 to 3 times per week with 10% to 20% dose increments. When asymptomatic, light pink erythema (Fig 1) lasting <24 hours is achieved, the optimal dose has been reached and treatment should continue at this dose until erythema disappears. The dose should then be increased again until it returns.²⁰ The maximum dose of NB-UVB varies depending on Fitzpatrick skin phototype and photosensitivity. There are no established guidelines for maximum dosing for vitiligo, and we therefore recommend increasing the dose until light pink erythema is achieved or until side effects (such as skin burning, sensitivity, peeling, or thickening) develop. A lack of response after 6 months suggests a nonresponsive patient, and discontinuation of treatment should be considered.¹¹

Targeted UVB phototherapy (level II)

Targeted phototherapy (excimer lasers and excimer lamps) can be considered when <10% of BSA is affected.² This therapy is attractive for patients who wish to avoid skin darkening caused by NB-UVB (Figs 2 and 3). Although effective in the repigmentation of stable lesions, this focal therapy



Fig 2. Vitiligo. Lesion on the lower leg before excimer laser treatment.



Fig 3. Vitiligo. Lesion on the lower leg (with pigmented hairs, which portend a favorable prognosis) after 7 months of excimer laser therapy.

typically fails to stabilize vitiligo because clinically unaffected skin is not treated. In the segmental variant, excimer laser seems to be the most beneficial treatment when used early in the disease course.²¹ In a recent retrospective study, 59 patients with the segmental variant, which is typically refractory to treatment, responded well to excimer laser, topical tacrolimus, and short-term systemic corticosteroids for 3 months; almost 50% of patients achieved >75% repigmentation.²²

Oral immunosuppression (level III-2 evidence)

Oral steroids may help stabilize rapidly progressive disease. Oral minipulse therapy (OMP) refers to the discontinuous administration of suprapharmacologic doses of steroids. Randomized controlled trials investigating their efficacy are still lacking, although numerous retrospective studies support their use in progressive disease. The regimen consists of low-dose betamethasone or dexamethasone for 3 to 6 months on 2 consecutive days. It is usually administered in combination with other therapies, including phototherapy.²³ In initial

reports, 5 mg betamethasone/dexamethasone was used on 2 consecutive days per week.^{24,25} This was increased to 7.5 mg/day in nonresponders and decreased back to 5 mg/day when disease progression was arrested. The results showed that 89% of patients were stabilized within 1 to 3 months. In another study, dexamethasone 10 mg twice weekly for ≤ 24 weeks halted disease progression in 88% of patients after 18.2 weeks.²⁶ However, 69% experienced side effects, including weight gain, insomnia, acne, agitation, menstrual irregularities, and hypertrichosis.

Other immunosuppressants and biologics

Limited data are available for the use of other immunosuppressant drugs in vitiligo. In a recent randomized comparative study, low-dose oral methotrexate was reported to be comparable to OMP, and suggested when OMP is contraindicated, although responses were marginal with small study sizes.²⁷

Anti-tumor necrosis factor- α drugs have been suggested for the treatment of vitiligo^{28,29} despite reports of no benefit and even initiation and worsening with their administration.³⁰⁻³⁴ Twice daily oral cyclophosphamide (50 mg) has also demonstrated repigmentation in 29 patients, including those with difficult to treat acral sites, although significant side effects were reported.³⁵ Although spontaneous remissions are uncommon in patients with vitiligo, treatment recommendations based on uncontrolled studies should be weighed against that possibility.

Other treatments

Vitamin D analogs (level III-I evidence). Most studies have evaluated calcipotriene in combination with other therapies, particularly phototherapy. Calcipotriene may shorten the time to achieve repigmentation and reduce overall cumulative exposure during phototherapy, but it has not demonstrated appreciable repigmentation when used alone.^{36,37}

Other treatments for vitiligo appeared to be promising in pilot trials but failed to demonstrate significant efficacy in later controlled trials. Examples include *Polypodium leucotomas*, ginkgo biloba, antioxidants, and pseudocatalase cream.³⁸

Comparative efficacy studies. *Topical steroids versus calcineurin inhibitors.* There have been a few studies comparing different treatments for vitiligo. In 1 study, tacrolimus ointment 0.1% was compared with clobetasol cream 0.05% in children.⁷ This randomized, double-blind, comparative trial revealed 49% repigmentation with clobetasol and 41% with tacrolimus, but the difference was not statistically

significant. Facial lesions responded best, with most patients tolerating treatment well. While small, this study provides evidence of efficacy for the treatment of vitiligo with tacrolimus (level of evidence I, strength of recommendation A).

Another study evaluated 100 children with vitiligo treated with tacrolimus, clobetasol, or placebo ointment.³⁹ The clobetasol-treated group received intermittent therapy and others continuous therapy; the clobetasol-treated group received clobetasol ointment for 2 months, petroleum jelly for the next 2 months, and clobetasol again for the remaining 2 months. The tacrolimus-treated group received 0.1% ointment for 6 months, and the placebo-treated group received petroleum jelly continuously for 6 months. There was no statistically significant difference between the tacrolimus and clobetasol groups, although facial lesions responded better than nonfacial lesions overall. Both treatments were superior to placebo (level of evidence I, strength of recommendation A).

A small study of 10 patients with bilaterally symmetrical generalized vitiligo treated with clobetasol cream on one side of the body and pimecrolimus cream on the other showed a comparable degree of repigmentation, although small numbers make noninferiority trials like this difficult to interpret.⁴⁰ (level of evidence II-I, strength of recommendation B).

NB-UVB versus PUVA. NB-UVB therapy has become the predominant form of phototherapy for vitiligo because of its efficacy, relative lack of side effects, and convenience. A study comparing 12 months of twice weekly NB-UVB to twice weekly oral 8-methoxypsoralen PUVA demonstrated superior repigmentation, color matching, and fewer side effects in the NB-UVB-treated group.¹¹ Overall, 64% of the NB-UVB group had $>50\%$ improvement in BSA affected versus 36% in the PUVA group. The superiority of NB-UVB was maintained 12 months after treatment ended (level of evidence I, strength of recommendation A).

Another investigator-blinded trial of NB-UVB versus PUVA 3 times per week for 6 months was conducted in 56 patients.⁴¹ Median repigmentation was similar between the 2 groups but adverse effects, particularly pruritus, were much lower in the NB-UVB group (7.4% vs 57.2%). The face, neck, and trunk demonstrated the best response in both groups (level of evidence I, strength of recommendation A).

Combination therapies. Although antioxidants have been promoted for various skin diseases, including vitiligo, few controlled studies have attempted to determine their true efficacy. In 1 randomized,



Fig 4. Vitiligo. Lesion on the upper aspect of the back before narrowband ultraviolet B light phototherapy.

double-blind, placebo-controlled study,⁴² patients received a combination of α -lipoic acid, vitamin C, vitamin E, and polyunsaturated fatty acids or placebo for 2 months. They were then treated with NB-UVB for 6 months. Forty-seven percent of those treated with antioxidants before NB-UVB demonstrated >75% repigmentation versus 18% in the placebo plus NB-UVB group. Although this is a single study, this controlled trial supports the use of antioxidants in patients undergoing phototherapy (level of evidence I, strength of recommendation A).

Evidence for treatment regimens. There is little evidence to guide clinicians on selecting the optimal frequency, dosing, and duration of treatment for vitiligo. No comparative studies have been performed on one topical dosing frequency versus another, 2 times weekly versus 3 times weekly phototherapy, or on different doses of oral corticosteroids for active vitiligo. Two have studied differences in efficacy between 2 and 3 times weekly treatments with the excimer laser for vitiligo.^{43,44} Both concluded that there was no difference in the final degree of repigmentation between the 2 dosing frequencies; however, repigmentation was dependent on the total number of treatment sessions, with earlier onset of pigmentation noted with 3 times weekly dosing. This is likely to be the case for NB-UVB also.

Regarding duration of therapy, a previous study reported a mean 25% improvement after 3 months, 50% after 6 months, and 75% after 9 months of NB-UVB therapy¹¹ (Figs 4 and 5). The slow but steady improvement when undergoing therapy for vitiligo requires patience and motivation on the part of the patient and clinician. Monitoring improvement requires baseline and serial images at each visit. As long as the patient is improving and side effects are tolerable, treatment can be continued until no further improvement occurs, after which maintenance treatment can be initiated.



Fig 5. Vitiligo. Lesion on the upper aspect of the back after 5 months of narrowband ultraviolet B light phototherapy.

Maintenance therapy. Given that the risk of relapse in the first year after ceasing therapy is 44%,⁴⁵ it may be important to transition patients to maintenance therapy once repigmentation is achieved. In 1 study, all patients achieving >75% repigmentation from any modality were treated with either tacrolimus ointment 0.1% or placebo ointment twice weekly. Thirty-five patients were enrolled in this 24-week trial.⁴⁶ Lesions on the hands and feet were excluded. Ninety-six percent of those treated with tacrolimus on the head and neck maintained the repigmented areas without relapse, while only 60% on placebo were maintained. Success of the maintenance therapy was independent of initial treatment modality. Topical tacrolimus ointment 0.1% twice weekly can therefore be recommended for maintenance therapy (level of evidence II; Figs 6 and 7). Some have suggested a similar approach with NB-UVB to prevent relapse, but no studies have tested the efficacy of this approach.

SURGICAL TECHNIQUES

Key points

- **Surgical techniques are most successful in late-stage segmental vitiligo**
- **Surgery can be considered in those with nonresponsive, stable vitiligo**
- **Noncultured epidermal melanocyte cell grafting demonstrates superior extent and quality of pigmentation compared with other surgical techniques**

Surgical treatments offer some of the best results for stable vitiligo. Repigmentation can improve by $\geq 68\%$ in certain types of vitiligo with only 1 treatment session.⁴⁷ When repigmentation is obtained in these patients, relapse is uncommon.^{48,49} Several surgical options exist, which can be classified



Fig 6. Vitiligo. Depigmented patch on buttock and scrotum of baby boy that repigmented with topical therapy.



Fig 7. Vitiligo. After 13 months of maintenance therapy with twice weekly tacrolimus, pigmentation has been maintained on the buttock and scrotum.

into tissue and cellular grafts. Tissue grafts usually transfer solid tissue from donor to recipient site in a 1:1 ratio. Cellular grafts cover larger surface areas and are composed of suspensions of keratinocytes and melanocytes in a donor to recipient ratio up to 1:10.

Patient selection

Patient selection is key to success with surgical treatment for vitiligo. Those with stable disease have a superior response to surgical intervention. Patients with segmental disease have better results than those with focal disease who, in turn, fare better than patients with generalized, unstable vitiligo.⁵⁰⁻⁵³

Disease stability must be evaluated before surgery and is defined by the absence of new or expanding lesions over 6 months to 2 years. Several methods can be used to assess stability, such as patient report, serial photography, and validated scoring systems. These include changes in the Vitiligo Area Scoring Index, Vitiligo European Task Force assessment, and Vitiligo Disease Activity Score. In cases where stability or treatment outcome is uncertain, performing a test procedure with a single punch graft in the center of a stable, depigmented lesion to assess the degree of repigmentation is useful.^{53,54}



Fig 8. Vitiligo. Lesion on left upper eyelid before treatment.



Fig 9. Vitiligo. Lesion on left upper eyelid 9 months after punch grafting. The hyperpigmentation and cobblestone appearance of the punch grafts usually subside with time.

Koebnerization, confetti-like lesions, inflammatory vitiligo, and trichome vitiligo are also indicators of unstable disease and are discussed in detail in the first article in this continuing medical education series.^{52,53}

Recipient site is another variable that should be considered. In general, the head and neck demonstrate a superior response.^{55,56} Acrofacial disease and areas over joints respond poorly, possibly because of repeated motion or friction and injury at these locations.^{55,56} Patients must be screened for a history of keloids, coagulation abnormalities, bloodborne infections, and other contraindications to surgery, such as severe heart disease.

Tissue grafts

Minipunch grafts are performed by placing 1- to 1.5-mm punch biopsy specimens from a donor site into a preprepared recipient site (Figs 8 and 9). This technically simple, inexpensive technique does not require specialized equipment but is difficult to perform on large areas, can lead to pigment and textural variations such as cobblestoning, and carries a risk of scarring and keloids.⁵⁷⁻⁶⁰



Fig 10. Vitiligo. Harvesting of suction blister grafts.

Suction blister epidermal grafting involves the creation and transfer of blister roofs from normal skin (Fig 10) to abraded depigmented skin. Advantages include low cost, use of simple equipment, uniform color match, low rates of scarring, and good efficacy. The time required to create blisters and risk of hemorrhagic blisters are disadvantages.^{57-59,61-63}

Cellular grafts

Cellular grafts can be cultured or noncultured and involve creating a cellular suspension from a thin to ultrathin skin graft. Noncultured options, although complex, do not require a full cell culture laboratory. Therefore, noncultured epidermal suspension (NCES) grafting, also known as a melanocyte keratinocyte transplant procedure, is performed more frequently than cultured melanocyte grafting. It is now considered the criterion standard for vitiligo grafting worldwide.

NCES is performed by harvesting an ultrathin skin graft from a donor site, which is then incubated in trypsin. After removal of the epidermis from the dermis, the epidermis is manually disrupted and then centrifuged to obtain the cellular pellet, which is resuspended in Ringers lactate, applied to the abraded recipient site, and dressed. Movement should be restricted postoperatively to avoid dressing displacement, but bed rest is not required. Dressings are removed between days 4 and 7. This procedure yields good cosmetic results and color match (Figs 11 and 12). Disadvantages include the cost, need for specialized equipment and a skilled team, and limitations of sites that can be successfully treated.^{47,51} A new method using epidermal suction blisters for donor skin has also been described.⁶⁴ Of note, battery-operated cell harvesting devices have also been developed, offering a self-contained system for cell separation without the need for additional equipment. Head to head comparison studies to standard NCES tissue processing techniques have not yet been performed.^{65,66}



Fig 11. Vitiligo. Segmental variant of vitiligo on the left upper forehead at baseline.

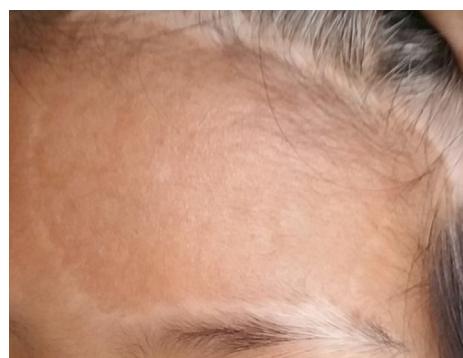


Fig 12. Vitiligo. Segmental variant of vitiligo on the left upper forehead 9 months after noncultured epidermal suspension grafting.

Comparative efficacy

NCES has shown superior extent and quality of repigmentation compared with blister grafting.⁶⁷ However, blister grafting and punch grafting are much easier techniques to master and require fewer support staff.

Camouflage techniques

Camouflage may be an important part of overall patient management given the aesthetic impact of the disease in many patients. Self-tanning agents provide waterproof protection for 3 to 5 days; highly pigmented cover creams require daily application but are lightweight and waterproof. While dermal pigmentation can be achieved with techniques like cosmetic tattooing, potential risks should be carefully considered. These risks include the potential for infection, risk of koebnerizing vitiligo, lack of legislation on tattoo pigments, poor color match, bleeding of color over time, and potential for spread of the lesion beyond the tattoo border.⁶⁸

TREATMENT ALGORITHM

Treatment for vitiligo should be started as early as possible to maximize efficacy. The type of vitiligo,

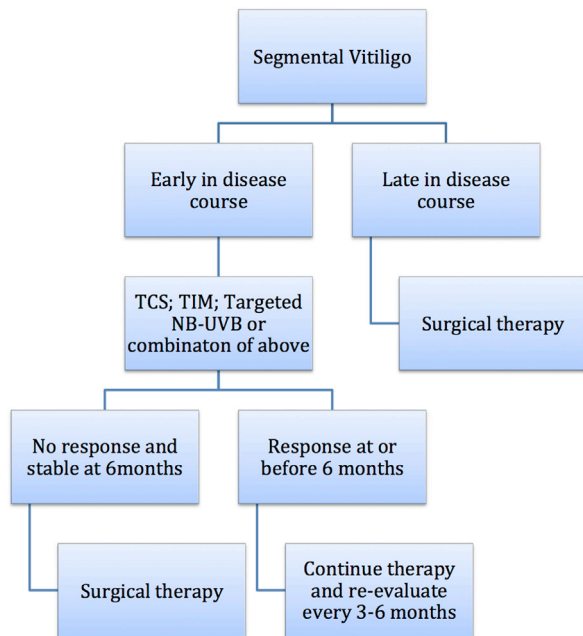


Fig 13. Treatment algorithm for the segmental variant of vitiligo. NB-UVB, Narrowband ultraviolet light phototherapy; TCS, topical corticosteroids; TIM, topical immunomodulators.

extent and duration of disease, effect on quality of life, and previous treatments should determine the initial treatment approach. The segmental variant, when treated early in the disease course (≤ 12 months), can be initially treated with skin-directed medical therapy. In nonresponsive or longstanding stable disease, surgical therapies should be considered (Fig 13).

The extent of involvement also determines the treatment approach in vitiligo. Localized disease (≤ 5 -10% of BSA) is best treated with topical therapy and targeted phototherapy, while a combination of NB-UVB and topical therapy is used to treat more extensive disease (> 5 -10% of BSA). OMP can be added for those with clinical signs of aggressive, progressive disease (Fig 14). Efficacy can be assessed at approximately 6 months based on twice-weekly NB-UVB.

TREATMENT SAFETY

Key points

- Topical corticosteroids, when used as directed and with dermatologic supervision, appear to be safe and are usually efficacious for vitiligo
- Despite evidence that tacrolimus does not appear to increase the risk of malignancy, its black box warning remains
- Long-term administration of NB-UVB does not appear to increase incidence of melanoma or nonmelanoma skin cancers in those with vitiligo

Topical therapies

Reported side effects of inappropriate or unsupervised topical steroids include cutaneous atrophy, telangiectasias, hypertrichosis, acne, and striae. However, its side effect profile has been deemed favorable when used as prescribed by dermatologists for atopic dermatitis, in which there is epidermal barrier dysfunction and a greater likelihood of systemic absorption.⁶⁹ To minimize the risk of side effects, a sequential discontinuous scheme may be used.

Topical tacrolimus lacks the side effect profile of topical steroids and appears to be much safer, particularly on sensitive areas like the face, genitals, and intertriginous sites. When topical tacrolimus first became available for use, concerns were raised about the risk of malignancies that had been observed in those taking large oral doses to prevent transplant organ rejection. However, a recent systematic review and metaanalysis reporting on the risk of lymphoma in those with atopic dermatitis concluded that it does not appear to significantly contribute to the overall risk of lymphoma in this subgroup of patients.⁷⁰ Nevertheless, this black box warning remains and it is still not approved by the FDA, Therapeutic Goods Administration (Australia), or the European Medicines Agency for use in vitiligo. If burning after application of tacrolimus is noted, the concentration may be decreased. While skin flushing may occur immediately after alcohol ingestion and is not always limited to the area of application, it resolves quickly.⁷¹

Phototherapy

While an absence of melanin in lesional skin and prolonged administration of phototherapy may give rise to concern about the development of skin cancer in this population, recent evidence suggests that the genetic and autoimmune profile of vitiligo patients confers a degree of protection against melanoma and nonmelanoma skin cancers (NMSCs).⁷²⁻⁷⁸ While prolonged PUVA for psoriasis increases the risk of cutaneous malignancies in white patients, the same has not been noted with NB-UVB.^{79,80} Even studies of PUVA for vitiligo do not appear to be associated with the development of NMSCs.^{81,82}

While Hexsel et al⁸³ reported a higher annual incidence of NMSC in those with vitiligo compared with the rest of the population, 5 other studies reveal lower rates of melanoma and NMSC in this population.⁸⁴⁻⁸⁸ In addition, a 2005 review of the literature suggested that chronic use of ultraviolet B light does not seem to increase the risk of skin cancer.⁸⁹ Limitations exist for all of these studies, highlighting the need for well-constructed

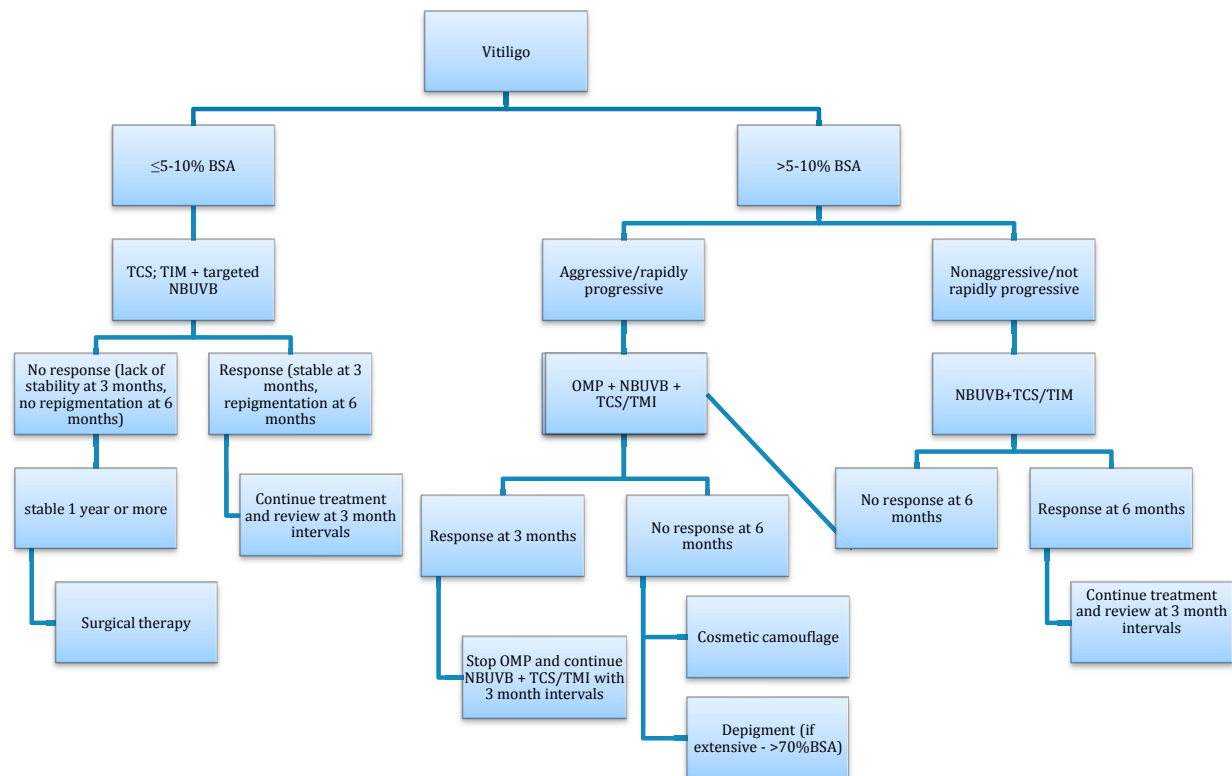


Fig 14. Treatment algorithm for vitiligo.

prospective randomized controlled trials that span decades.

Surgical treatments

Complications are rare with most surgical procedures but include pain, hypopigmentation, koebnerization, scarring, and infection.^{47,60}

EMERGING TREATMENT MODALITIES

Key points

- **Afamelanotide enhances the efficacy of NB-UVB in patients with vitiligo**
- **Targeted immunotherapy has been safe and effective for psoriasis, and a similar treatment strategy may be equally beneficial for vitiligo patients**
- **The interferon- γ -CXCL10 chemokine axis appears to be an important target for the development of new treatments for vitiligo**

α -Melanocyte-stimulating hormone analogues

Afamelanotide is a potent synthetic analogue of the naturally occurring α -melanocyte-stimulating hormone. It was investigated as an adjunct to NB-UVB in a double blind, multicenter study. Patients treated with NB-UVB plus afamelanotide versus NB-UVB alone achieved repigmentation rates

of 48.64% and 33.26% at day 168, respectively. Side effects included hyperpigmentation, itch, and nausea.⁹⁰ Additional studies with this promising treatment are warranted.

Targeted immunotherapy

In the first article in this series, we outlined recent translational research that has provided insight into possible targets for targeted therapies for vitiligo. In particular, interfering with the interferon (IFN)- γ -CXCL10 chemokine axis may be an effective strategy to develop novel, targeted immunotherapies.⁹¹ Significant repigmentation of 2 patients after the oral administration of tofacitinib⁹² (a pan-Janus kinase inhibitor [JAK 1/3]) and ruxolitinib⁹³ (JAK 1/2 inhibitor), which directly inhibit IFN- γ signaling, supports this concept. However, repigmentation regressed when the patient discontinued ruxolitinib, suggesting that continuous treatment is required. Importantly, the patient's serum CXCL10 level was reduced during treatment with ruxolitinib, suggesting that JAK inhibition works by targeting the IFN- γ -CXCL10 axis, and that it may serve as a biomarker for disease activity and treatment response. A recent case series reported efficacy of topical ruxolitinib in patients with vitiligo, particularly on the face.⁹⁴ While these

advances are promising for vitiligo sufferers and dermatologists alike, larger, controlled studies are required to assess the safety and efficacy of targeted therapies for vitiligo.

Depigmentation

For patients with recalcitrant and widespread (>50% of BSA) vitiligo, depigmentation of the remaining islands of pigment may provide cosmetic improvement that may enhance quality of life. Following its discovery in rubber gloves⁹⁵ more than 50 years ago, monobenzyether of hydroquinone (MBEH) has become the most commonly used depigmentation therapy for vitiligo and is currently the only drug approved by the FDA for the treatment of vitiligo in the United States. Depigmentation should only be considered after psychological screening and informed consent about the irreversible nature of the treatment. Patients should be aware that depigmentation cannot be targeted to a single location, but local application frequently depigments the entire skin. MBEH is applied in a 20% concentration twice daily to pigmented skin, and care should be taken to avoid excessive sun exposure, which can result in perifollicular repigmentation. The most common side effect is irritant contact dermatitis, which may be treatment-limiting,⁹⁶ and rarely ocular side effects have been reported, such as conjunctival melanosis.⁹⁷

Complete depigmentation may require 4 to 12 months of therapy with potentially longer durations required in patients with skin of color. The concentration can be increased to 30% if responses are not noted after 4 months of treatment, but treatment should be discontinued if no response is seen at 6 months. Once depigmentation is achieved, MBEH can be used a few times per week as maintenance if required.

Recalcitrant areas of pigmentation postdepigmentation therapy may be treated with quality-switched 694-nm laser⁹⁸ alone or in combination with methoxyphenol.⁹⁹ Mequinol is a phenol derivative thought to produce similar results to MBEH but with a slower onset of depigmentation. Laser and cryotherapy¹⁰⁰ have also been tested in Europe, where the use of MBEH has been restricted.

SUMMARY

Although it is usually slow to respond and repigmentation may not always occur despite intensive treatment, the variety of management options should be presented to patients who seek treatment. A 2-pronged approach combining stabilization of the disease by reducing the

autoimmune destruction of melanocytes along with stimulation of melanocyte regeneration is likely to produce the best results. Lack of previous success is often the reason for a pessimistic outlook regarding treatment on the part of both the treating physician and the patient; however, education and establishing realistic expectations, a comprehensive treatment plan, and photography at each visit can result in a successful outcome. Recent advances in determining the pathogenesis of the disease have opened exciting new treatment avenues that may herald a revolution in the future treatment of vitiligo.

REFERENCES

1. Ezzedine K, Sheth V, Rodrigues M, et al. Vitiligo is not a cosmetic disease. *J Am Acad Dermatol*. 2015;73:883-885.
2. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015;386:74-84.
3. Gan EY, Cario-Andre M, Pain C, et al. Follicular vitiligo: a report of 8 cases. *J Am Acad Dermatol*. 2016;74:1178-1184.
4. Stinco G, Trevisan G, Buligan C, et al. Narrow band-ultraviolet B versus clobetasol propionate foam in the treatment of vitiligo: a retrospective study. *Dermatol Ther*. 2013;3:95-105.
5. Taieb A, Alomar A, Bohm M, et al. Guidelines for the management of vitiligo: the European Dermatology Forum consensus. *Br J Dermatol*. 2013;168:5-19.
6. Whitton ME, Pinart M, Batchelor J, et al. Interventions for vitiligo. *Cochrane Database Syst Rev*. 2015;2:CD003263.
7. Lepe V, Moncada B, Castaneda-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. *Arch Dermatol*. 2003;139:581-585.
8. Mehrabi D, Pandya AG. A randomized, placebo-controlled, double-blind trial comparing narrowband UV-B Plus 0.1% tacrolimus ointment with narrowband UV-B plus placebo in the treatment of generalized vitiligo. *Arch Dermatol*. 2006;142:927-929.
9. Rath N, Kar HK, Sabhnani S. An open labeled, comparative clinical study on efficacy and tolerability of oral minipulse of steroid (OMP) alone, OMP with PUVA and broad/narrowband UVB phototherapy in progressive vitiligo. *Indian J Dermatol Venereol Leprol*. 2008;74:357-360.
10. Bhatnagar A, Kanwar AJ, Parsad D, De D. Psoralen and ultraviolet A and narrow-band ultraviolet B in inducing stability in vitiligo, assessed by vitiligo disease activity score: an open prospective comparative study. *J Eur Acad Dermatol Venereol*. 2007;21:1381-1385.
11. Yones SS, Palmer RA, Garibaldinos TM, Hawk JL. Randomized double-blind trial of treatment of vitiligo: efficacy of psoralen-UV-A therapy vs narrowband-UV-B therapy. *Arch Dermatol*. 2007;143:578-584.
12. Bhatnagar A, Kanwar AJ, Parsad D, De D. Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: an open prospective study. *J Eur Acad Dermatol Venereol*. 2007;21:638-642.
13. Pathak MA, Mosher DB, Fitzpatrick TB. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5',8-trimethylpsoralen, and psoralen in vitiligo. *Natl Cancer Inst Monogr*. 1984;66:165-173.
14. De Francesco V, Stinco G, Laspinia S, Parlangeli ME, Mariuzzi L, Patrone P. Immunohistochemical study before and after narrow band (311 nm) UVB treatment in vitiligo. *Eur J Dermatol*. 2008;18:292-296.

15. Arca E, Tastan HB, Erbil AH, Sezer E, Koc E, Kurumlu Z. Narrow-band ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of vitiligo. *J Dermatol*. 2006;33:338-343.
16. Welsh O, Herz-Ruelas ME, Gomez M, Ocampo-Candiani J. Therapeutic evaluation of UVB-targeted phototherapy in vitiligo that affects less than 10% of the body surface area. *Int J Dermatol*. 2009;48:529-534.
17. Kanwar AJ, Dogra S. Narrow-band UVB for the treatment of generalized vitiligo in children. *Clin Exp Dermatol*. 2005;30:332-336.
18. Kanwar AJ, Dogra S, Parsad D, Kumar B. Narrow-band UVB for the treatment of vitiligo: an emerging effective and well-tolerated therapy. *Int J Dermatol*. 2005;44:57-60.
19. Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *J Am Acad Dermatol*. 2000;42:245-253.
20. Mohammad TF, Al-Jamal M, Hamzavi IH, et al. The vitiligo working group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo. *J Am Acad Dermatol*. 2017;76:879-888.
21. Do JE, Shin JY, Kim DY, Hann SK, Oh SH. The effect of 308nm excimer laser on segmental vitiligo: a retrospective study of 80 patients with segmental vitiligo. *Photodermatol Photoimmunol Photomed*. 2011;27:147-151.
22. Bae JM, Yoo HJ, Kim H, Lee JH, Kim GM. Combination therapy with 308-nm excimer laser, topical tacrolimus, and short-term systemic corticosteroids for segmental vitiligo: a retrospective study of 159 patients. *J Am Acad Dermatol*. 2015;73:76-82.
23. Kanwar AJ, Mahajan R, Parsad D. Low-dose oral mini-pulse dexamethasone therapy in progressive unstable vitiligo. *J Cutan Med Surg*. 2013;17:259-268.
24. Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast-spreading disease. *Int J Dermatol*. 1993;32:753-757.
25. Pasricha JS, Seetharam KA, Dashore A. Evaluation of five different regimes for the treatment of vitiligo. *Indian J Dermatol Venereol Leprol*. 1989;55:18-21.
26. Radakovic-Fijan S, Furnsinn-Friedl AM, Honigsman H, Tanew A. Oral dexamethasone pulse treatment for vitiligo. *J Am Acad Dermatol*. 2001;44:814-817.
27. Singh H, Kumaran MS, Bains A, Parsad D. A randomized comparative study of oral corticosteroid minipulse and low-dose oral methotrexate in the treatment of unstable vitiligo. *Dermatology*. 2015;231:286-290.
28. Kim NH, Torchia D, Rouhani P, Roberts B, Romanelli P. Tumor necrosis factor- α in vitiligo: direct correlation between tissue levels and clinical parameters. *Cutan Ocul Toxicol*. 2011;30:225-227.
29. Webb KC, Tung R, Winterfield LS, et al. Tumour necrosis factor- α inhibition can stabilize disease in progressive vitiligo. *Br J Dermatol*. 2015;173:641-650.
30. Alghamdi KM, Khurram H, Taieb A, Ezzedine K. Treatment of generalized vitiligo with anti-TNF- α agents. *J Drugs Dermatol*. 2012;11:534-539.
31. Maruthappu T, Leandro M, Morris SD. Deterioration of vitiligo and new onset of halo naevi observed in two patients receiving adalimumab. *Dermatol Ther*. 2013;26:370-372.
32. Alghamdi KM, Khurram H, Rikabi A. Worsening of vitiligo and onset of new psoriasiform dermatitis following treatment with infliximab. *J Cutan Med Surg*. 2011;15:280-284.
33. Speeckaert R, Speeckaert MM, van Geel N. Why treatments do(n't) work in vitiligo: an autoinflammatory perspective. *Autoimmun Rev*. 2015;14:332-340.
34. Rigopoulos D, Gregoriou S, Larios G, Moustou E, Belayeva-Karatza E, Kalogeromitros D. Etanercept in the treatment of vitiligo. *Dermatology*. 2007;215:84-85.
35. Gokhale BB. Cyclophosphamide and vitiligo. *Int J Dermatol*. 1979;18:92.
36. Goktas EO, Aydin F, Senturk N, Canturk MT, Turanli AY. Combination of narrow band UVB and topical calcipotriol for the treatment of vitiligo. *J Eur Acad Dermatol Venereol*. 2006;20:553-557.
37. Ermis O, Alpsoy E, Cetin L, Yilmaz E. Is the efficacy of psoralen plus ultraviolet A therapy for vitiligo enhanced by concurrent topical calcipotriol? A placebo-controlled double-blind study. *Br J Dermatol*. 2001;145:472-475.
38. Cohen BE, Elbuluk N, Mu EW, Orlow SJ. Alternative systemic treatments for vitiligo: a review. *Am J Clin Dermatol*. 2015;16:463-474.
39. Ho N, Pope E, Weinstein M, Greenberg S, Webster C, Krafchik BR. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs. clobetasol propionate 0.05% in childhood vitiligo. *Br J Dermatol*. 2011;165:626-632.
40. Coskun B, Saral Y, Turgut D. Topical 0.05% clobetasol propionate versus 1% pimecrolimus ointment in vitiligo. *Eur J Dermatol*. 2005;15:88-91.
41. Sapam R, Agrawal S, Dhali TK. Systemic PUVA vs. narrowband UVB in the treatment of vitiligo: a randomized controlled study. *Int J Dermatol*. 2012;51:1107-1115.
42. Dell'Anna ML, Mastrofrancesco A, Sala R, et al. Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial. *Clin Exp Dermatol*. 2007;32:631-636.
43. Hofer A, Hassan AS, Legat FJ, Kerl H, Wolf P. Optimal weekly frequency of 308-nm excimer laser treatment in vitiligo patients. *Br J Dermatol*. 2005;152:981-985.
44. Shen Z, Gao TW, Chen L, et al. Optimal frequency of treatment with the 308-nm excimer laser for vitiligo on the face and neck. *Photomed Laser Surg*. 2007;25:418-427.
45. 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;56:274-278.
46. Cavalie M, Ezzedine K, Fontas E, et al. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo-controlled study. *J Invest Dermatol*. 2015;135:970-974.
47. Huggins RH, Henderson MD, Mulekar SV, et al. Melanocyte-keratinocyte transplantation procedure in the treatment of vitiligo: the experience of an academic medical center in the United States. *J Am Acad Dermatol*. 2012;66:785-793.
48. Gan EY, Kong YL, Tan WD, Thng ST, Goh BK. Twelve-month and sixty-month outcomes of noncultured cellular grafting for vitiligo. *J Am Acad Dermatol*. 2016;75:564-571.
49. van Geel N, Wallaey E, Goh BK, De Mil M, Lambert J. Long-term results of noncultured epidermal cellular grafting in vitiligo, halo naevi, piebaldism and naevus depigmentosus. *Br J Dermatol*. 2010;163:1186-1193.
50. Khunger N, Kathuria SD, Ramesh V. Tissue grafts in vitiligo surgery - past, present, and future. *Indian J Dermatol*. 2009;54:150-158.
51. Mulekar SV. Melanocyte-keratinocyte cell transplantation for stable vitiligo. *Int J Dermatol*. 2003;42:132-136.
52. Njoo MD, Das PK, Bos JD, Westerhof W. Association of the Koebner phenomenon with disease activity and therapeutic responsiveness in vitiligo vulgaris. *Arch Dermatol*. 1999;135:407-413.

53. Falabella R. The minigrafting test for vitiligo: validation of a predicting tool. *J Am Acad Dermatol*. 2004;51:672-673.
54. Falabella R, Arrunategui A, Barona MI, Alzate A. The minigrafting test for vitiligo: detection of stable lesions for melanocyte transplantation. *J Am Acad Dermatol*. 1995;32:228-232.
55. Mulekar SV, Isedeh P. Surgical interventions for vitiligo: an evidence-based review. *Br J Dermatol*. 2013;169(suppl 3):57-66.
56. Gupta S. *Surgical Management of Vitiligo*. Malden (MA): Blackwell Publishers; 2007.
57. Feetham HJ, Chan JL, Pandya AG. Characterization of clinical response in patients with vitiligo undergoing autologous epidermal punch grafting. *Dermatol Surg*. 2012;38:14-19.
58. Gupta S, Ajith C, Kanwar AJ, Kumar B. Surgical pearl: standardized suction syringe for epidermal grafting. *J Am Acad Dermatol*. 2005;52:348-350.
59. Gupta S, Chandrashekar BS, Reddy R, Jagadish P, Asati D. Rapid induction of suction blisters by intra-cavity positive pressure enhancement. *Dermatol Surg*. 2011;37:843-845.
60. Al-Hadidi N, Griffith JL, Al-Jamal MS, Hamzavi I. Role of recipient-site preparation techniques and post-operative wound dressing in the surgical management of vitiligo. *J Cutan Aesthet Surg*. 2015;8:79-87.
61. Agrawal K, Agrawal A. Vitiligo: repigmentation with dermabrasion and thin split-thickness skin graft. *Dermatol Surg*. 1995;21:295-300.
62. Malakar S, Malakar RS. Surgical pearl: composite film and graft unit for the recipient area dressing after split-thickness skin grafting in vitiligo. *J Am Acad Dermatol*. 2001;44:856-858.
63. Krishnan A, Kar S. Smashed skin grafting or smash grafting - a novel method of vitiligo surgery. *Int J Dermatol*. 2012;51:1242-1247.
64. Jeong HS, Vandergriff T, Pandya AG. Use of suction blisters for noncultured epidermal suspension grafting in patients with vitiligo. *Dermatol Surg*. 2016;42:688-691.
65. Mulekar SV, Ghwish B, Al Issa A, Al Eisa A. Treatment of vitiligo lesions by ReCell vs. conventional melanocyte-keratinocyte transplantation: a pilot study. *Br J Dermatol*. 2008;158:45-49.
66. Komen L, Vrijman C, Tjin EP, et al. Autologous cell suspension transplantation using a cell extraction device in segmental vitiligo and piebaldism patients: a randomized controlled pilot study. *J Am Acad Dermatol*. 2015;73:170-172.
67. Budania A, Parsad D, Kanwar AJ, Dogra S. Comparison between autologous noncultured epidermal cell suspension and suction blister epidermal grafting in stable vitiligo: a randomized study. *Br J Dermatol*. 2012;167:1295-1301.
68. De Cuyper C. Permanent makeup: indications and complications. *Clin Dermatol*. 2008;26:30-34.
69. Mooney E, Rademaker M, Dailey R, et al. Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement. *Australas J Dermatol*. 2015;56:241-251.
70. Legendre L, Barnette T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;72:992-1002.
71. Milingou M, Antille C, Sorg O, Saurat JH, Lubbe J. Alcohol intolerance and facial flushing in patients treated with topical tacrolimus. *Arch Dermatol*. 2004;140:1542-1544.
72. Jin Y, Birlea SA, Fain PR, et al. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *N Engl J Med*. 2010;362:1686-1697.
73. Bishop DT, Demenais F, Iles MM, et al. Genome-wide association study identifies three loci associated with melanoma risk. *Nat Genet*. 2009;41:920-925.
74. Liu JB, Li M, Chen H, et al. Association of vitiligo with HLA-A2: a meta-analysis. *J Eur Acad Dermatol Venereol*. 2007;21:205-213.
75. Alonso-Castro L, Rios-Buceta L, Vano-Galvan S, Moreno C, Soria-Rivas A, Jaen P. Vitiligo in 2 patients receiving vemurafenib for metastatic melanoma. *J Am Acad Dermatol*. 2013;69:e28-e29.
76. Mochel MC, Ming ME, Imadojemu S, et al. Cutaneous autoimmune effects in the setting of therapeutic immune checkpoint inhibition for metastatic melanoma. *J Cutan Pathol*. 2016;43:787-791.
77. Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol*. 2016;152:45-51.
78. Rodrigues M. Skin cancer risk (nonmelanoma skin cancer/s/melanoma) in vitiligo patients. *Dermatol Clin*. 2017;35:129-134.
79. Hearn RM, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol*. 2008;159:931-935.
80. Weischer M, Blum A, Eberhard F, Rocken M, Berneburg M. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Derm Venereol*. 2004;84:370-374.
81. Wildfang IL, Jacobsen FK, Thestrup-Pedersen K. PUVA treatment of vitiligo: a retrospective study of 59 patients. *Acta Derm Venereol*. 1992;72:305-306.
82. Halder RM, Battle EF, Smith EM. Cutaneous malignancies in patients treated with psoralen photochemotherapy (PUVA) for vitiligo. *Arch Dermatol*. 1995;131:734-735.
83. Hexsel CL, Eide MJ, Johnson CC, et al. Incidence of nonmelanoma skin cancer in a cohort of patients with vitiligo. *J Am Acad Dermatol*. 2009;60:929-933.
84. Lindelof B, Hedblad MA, Sigurgeirsson B. On the association between vitiligo and malignant melanoma. *Acta Derm Venereol*. 1998;78:483-484.
85. Schallreuter KU, Tobin DJ, Panske A. Decreased photodamage and low incidence of non-melanoma skin cancer in 136 sun-exposed caucasian patients with vitiligo. *Dermatology*. 2002;204:194-201.
86. 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. *Br J Dermatol*. 2013;168:162-171.
87. Park KK, Murase JE, Koo J. Long-term prognosis of vitiligo patients on narrowband UVB phototherapy. *J Am Acad Dermatol*. 2012;66:326-327.
88. Paradisi A, Tabolli S, Didona B, Sobrino L, Russo N, Abeni D. Markedly reduced incidence of melanoma and nonmelanoma skin cancer in a nonconcurrent cohort of 10,040 patients with vitiligo. *J Am Acad Dermatol*. 2014;71:1110-1116.
89. Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. *Int J Dermatol*. 2005;44:355-360.
90. Lim HW, Grimes PE, Agbai O, et al. Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. *JAMA Dermatol*. 2015;151:42-50.

91. Rashighi M, Harris JE. Interfering with the IFN-gamma/CXCL10 pathway to develop new targeted treatments for vitiligo. *Ann Transl Med*. 2015;3:343.
92. King BA, Craiglow BG. Tofacitinib citrate for the treatment of vitiligo: A pathogenesis-directed therapy. *JAMA Dermatol*. 2015;151(10):1110-1112.
93. Harris JE, Rashighi M, Nguyen N, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J Am Acad Dermatol*. 2016;74:370-371.
94. Rothstein B, Joshipura D, Saraiya A, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;76:1054-1060.
95. Oliver EA, Schwartz L, Warren LH. Occupational leukoderma. *Arch Dermatol*. 1940;42:993-1014.
96. Nordlund JJ, Forget B, Kirkwood J, Lerner AB. Dermatitis produced by applications of monobenzone in patients with active vitiligo. *Arch Dermatol*. 1985;121:1141-1144.
97. Hedges TR 3rd, Kenyon KR, Hanninen LA, Mosher DB. Corneal and conjunctival effects of monobenzone in patients with vitiligo. *Arch Ophthalmol*. 1983;101:64-68.
98. Kim YJ, Chung BS, Choi KC. Depigmentation therapy with Q-switched ruby laser after tanning in vitiligo universalis. *Dermatol Surg*. 2001;27:969-970.
99. Solano F, Briganti S, Picardo M, Ghanem G. Hypopigmenting agents: an updated review on biological, chemical and clinical aspects. *Pigment Cell Res*. 2006;19:550-571.
100. AlGhamdi KM, Kumar A. Depigmentation therapies for normal skin in vitiligo universalis. *J Eur Acad Dermatol Venereol*. 2011;25:749-757.

Answers to CME examination

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