
Vitiligo: A comprehensive overview

Part II: Treatment options and approach to treatment

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Vitiligo is a common skin disorder that results in depigmentation. With the appropriate management, many patients can minimize disease progression, attain repigmentation, and achieve cosmetically pleasing results. There are numerous medical and surgical treatments aimed at repigmentation; therapies for depigmentation are available for patients with recalcitrant or advanced disease. The use of cosmetics at all stages of treatment may be vital to the patient's quality of life. Understanding all the available options helps choose the appropriate treatment plan and tailor it to your patient. Part II of this two-part series on vitiligo discusses the indications for, evidence behind, and adverse effects associated with many of the therapies used for vitiligo. Both conventional medical and surgical options are discussed in addition to several alternative and promising new therapies. (J Am Acad Dermatol 2011;65:493-514.)

Key words: antioxidants; autoimmune; autologous melanocyte suspension graft; biologic agents; camouflage; corticosteroids; chemophototherapy; depigmentation; depigmented; hypopigmentation; hypopigmented; laser; leukoderma; macule; melanocyte; melanosome; phototherapy; psychotherapy; punch graft; split thickness skin graft; suction blister graft; topical calcineurin inhibitors; vitamin D3 analogs; vitiligo.

Key points

- Many different modalities—both conventional and alternative and non-surgical and surgical—are used to treat vitiligo
- For patients with extensive or recalcitrant disease, treatments are aimed at depigmentation and/or camouflage

Vitiligo can be socially and psychologically devastating. Because there is currently no known cure, treatment is aimed at halting disease progression, inducing repigmentation, and achieving an acceptable cosmetic result. This paper reviews treatment the modalities currently available for patients with vitiligo and evaluates their efficacy in comparison to one another through a comprehensive literature review. Conventional nonsurgical and surgical therapies are discussed along with alternative and promising new treatments. Despite treatment, many patients will continue to suffer with vitiligo throughout their entire lives. For this reason, methods for coping with lifelong disease are addressed as an adjunct for those with recalcitrant disease.

INDIVIDUAL PROGNOSTIC FACTORS

Key points

- Mucosal involvement, a family history of vitiligo, koebnerization, and nonsegmental

CAPSULE SUMMARY

- Numerous treatment options exist for vitiligo, but there is no cure.
- Nonsurgical treatments include topical, systemic, phototherapy, photochemotherapy, and laser therapy.
- Surgical options include skin grafting and melanocyte suspension transplantation.
- Alternative therapies, camouflage, psychotherapy, and depigmentation can be beneficial to patients with vitiligo.
- Treatment efficacy varies with duration and distribution of disease, type of vitiligo, and use in combination with other modalities.

vitiligo are associated with disease progression in patients not receiving therapy

- Younger patients, those with recent onset of disease, darker skin types, and lesions of the face, neck, and trunk tend to respond best to therapy

Counseling patients on therapeutic options should create realistic expectations. Understanding the factors that may affect a patient's prognosis and response to treatment is essential for success. In general, patients with a family history of vitiligo, mucosal involvement, a positive

Koebner response, and the nonsegmental subtype of vitiligo (NSV) tend to have progression of their condition in the absence of therapy.¹ The best response to treatment is seen in younger patients, disease of recent onset, darker skin types, and in lesions on the face, neck, and trunk. Distal extremities tend to be extremely refractory to nonsurgical modalities.²⁻⁷

CORTICOSTEROIDS

Key points

- Topical corticosteroids are common first-line and adjunctive therapies
- Topical corticosteroids are the most effective monotherapy and produce the best clinical outcomes when combined with light therapy
- Systemic corticosteroids effectively halt disease progression and induce repigmentation; however, safety profiles and optimal dosing parameters are lacking
- Side effects of corticosteroids limit treatment; regular steroid holidays are recommended

Background

Corticosteroids (CSs) are commonly used as a first-line and adjunctive therapy for the treatment of vitiligo. Their efficacy is attributed to modulation of

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the immune response. Studies have shown an abundance of inflammatory cells in vitiligo, with a predominance of macrophages and T cells.^{8,9} Elevated autoantibody and complement-mediated melanocyte destruction has also been reported.¹⁰ Treatment with CSs decreases this destruction¹⁰ and appears to induce melanocyte repopulation and melanin production in vitiliginous skin.¹¹

Efficacy of topical corticosteroids

Placebo studies have supported the efficacy of CS monotherapy.¹² Higher response rates are seen in children compared to adults²; head and neck lesions tend to have the greatest response to treatment.^{2,3} In a review of 101 children treated with topical CSs alone, Kwinter et al¹³ reported response rates of 64%. Complete repigmentation rates have been reported to be as high as 49.3%.¹⁴

Based on comparative studies, topical CSs are the most clinically effective choice for topical therapy. Compared with topical calcineurin inhibitors, patients treated with topical CSs had equivocal to slightly higher rates of repigmentation.^{14,15} Westerhof et al⁶ found similar rates of repigmentation with topical fluticasone as with ultraviolet A light (UVA) phototherapy.¹⁶ When used in conjunction with UVA phototherapy, fluticasone enhanced repigmentation rates approximately threefold compared to either as monotherapy.¹⁶

Efficacy of systemic corticosteroids

Systemic CSs, although they are currently not considered conventional treatment for vitiligo, can be effective through inducing immunosuppression. There are few large studies that have evaluated their safety and efficacy. Seiter et al¹⁷ found that administering methylprednisolone 8 mg/kg intravenously for 3 days in patients with generalized vitiligo led to cessation of disease progression in 85% and repigmentation in 71%. Dexamethasone 10 mg intravenously for 2 consecutive days per week for up to 24 weeks showed a similar degree of halting disease progression, but induced repigmentation in only 37.6%.¹⁸ Similar response rates have been confirmed by other studies,¹⁹ with repigmentation rates as high as 75% (in 5% of subjects).²⁰ When used as an adjunct to phototherapy, oral pulse dose steroids achieve the highest repigmentation response with narrowband ultraviolet B light (NB-UVB) phototherapy compared to both psoralen plus UVA and broadband UVB phototherapies.²⁰

Safety

One of the biggest factors limiting the use of CSs is the concern for side effects. Side effects of topical



Fig 1. Steroid folliculitis developed with daily application of clobetasol propionate 0.05% ointment for 3 weeks in a patient with treatment-naïve segmental vitiligo.

therapy include epidermal atrophy, telangiectasia, striae distensae, steroid folliculitis (Fig 1), and side effects associated with systemic absorption.^{13,14} In children treated with medium to high potency topical CSs, 26% developed local side effects, and 29% had abnormal cortisol levels at follow-up. Cortisol levels were more affected when treating lesions on the head and neck, and, interestingly, did not correlate with steroid potency.¹³

Systemic CSs may induce insomnia, acne, agitation, menstrual disturbances, weight gain, hypertrichosis, and adrenal insufficiency. In one study of vitiligo patients treated with intravenous steroids, 69% reported systemic side effects.¹⁸ While systemic CSs have potential in treating patients with vitiligo, the lack of data on efficacy and optimal dosing parameters warrant further research.

Recommendations

Topical CSs are generally considered a safe first-line therapy. Head and neck lesions have the best response rates, but there is concern for systemic absorption. Local side effects may prohibit long-term use and merit frequent monitoring and regular steroid holidays. Systemic CSs can halt disease progression and induce repigmentation in patients with progressive vitiligo. However, their efficacy, safety, and optimal dosing parameters remain to be determined. Regardless of route, combining CSs with light therapy appears to enhance the results.

TOPICAL CALCINEURIN INHIBITORS

Key points

- Topical calcineurin inhibitors provide similar to slightly inferior results compared to topical corticosteroids

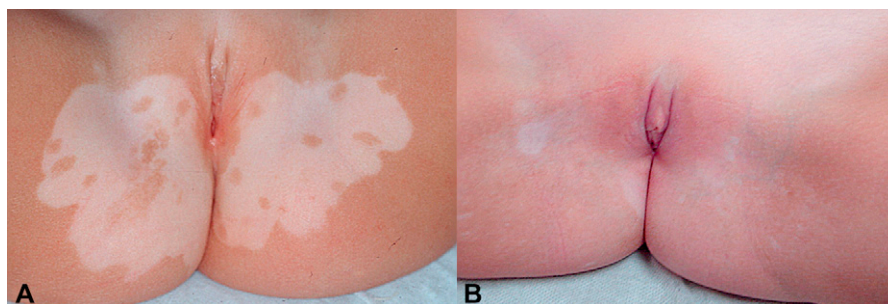


Fig 2. A 2-year-old girl with vitiligo was treated with topical tacrolimus 0.1% cream daily for 6 months followed by 3 times a week for another 6 months (A) before treatment and (B) 1 year after treatment completion. (Courtesy of Dr Tania Cestari, University of Rio Grande do Sul, HCPA Brazil, Department of Dermatology.)

- **Calcineurin inhibitors enhance the effect of light/laser therapy**
- **Topical calcineurin inhibitors are considered safe for short-term or intermittent long-term use**

Background

Calcineurin inhibitors (CIs) are advantageous in treating vitiligo because they have immunomodulatory effects without the side effect profile of CSs. Calcineurin is an intracellular protein in lymphocytes and dendritic cells. When activated, it acts as a transcription factor for cytokines, such as interleukin-2 (IL-2) and tumor necrosis factor- α (TNF α).²¹ Compared to healthy controls, patients with vitiligo have elevated IL-10, TNF α , and interferon-gamma. Treatment with tacrolimus decreases tissue counts of TNF α ²² and enhances melanocyte and melanoblast proliferation.²³ While there are little data on the use of systemic cyclosporine in the treatment of vitiligo, both topical pimecrolimus and tacrolimus have been used with success.

Efficacy

Many small clinical studies support the efficacy of topical tacrolimus and pimecrolimus when assessed after 3 and 6 months of therapy. Response rates range from 63% to 89%,^{6,22,24-26} with the best results seen on the head and neck (Fig 2).^{6,24,25} Mean repigmentation rates range from 26% to 72.5%.^{27,28} Nightly occlusion may enhance the effect on arm and leg lesions that were previously nonresponsive to topical therapy.^{25,29}

Compared to topical CSs, CIs produce slightly inferior to equivalent repigmentation rates,^{14,15} but the effect occurs earlier in the course of treatment.³⁰

Topical CIs work well as adjunctive therapy. Although a small randomized, double-blinded placebo controlled trial found no benefit for adding

topical tacrolimus to NB-UVB phototherapy,³¹ others have shown repigmentation rates of more than 50% in 42% of lesions in patients with chronic stable refractory vitiligo³² and that combination therapy can provide additional benefit for facial lesions.³³ Studies combining topical tacrolimus with the 308-nm excimer laser have shown even more promising results. Passeron et al³⁴ found that combining tacrolimus with a 308-nm laser therapy produced a 100% response rate, with 70% achieving more than 75% repigmentation, compared to light only, which had response and more than 75% repigmentation rates of 85% and 20%, respectively. The delay to onset of repigmentation was shorter in lesions treated with combination therapy.

Safety

Topical CIs are safe for short-term or intermittent long-term use. Common side effects include erythema, pruritis, burning, and irritation^{6,14,22,24,31}; hyperpigmentation and acne are less frequent.³⁵⁻³⁷ As a precautionary measure, the product label revisions approved by the US Food and Drug Administration (FDA) for topical CIs in January 2006 were based on a theoretical risk arising from the systemic use of CIs in transplant recipients and animal studies. This is a controversial issue, and data have yet to support the link between topical CIs and cancer.³⁸ Extensive safety data have been analyzed from more than 20,000 clinical trial participants using tacrolimus ointment. To date, there is no evidence to suggest that there is an increased risk of lymphoma or nonmelanoma skin cancer in adults or children using tacrolimus ointment.³⁹

Recommendations

Topical CIs are approved by the FDA for short-term (2-4 weeks) or intermittent long-term use in patients with atopic dermatitis⁴⁰; however, the off-label use of pimecrolimus and tacrolimus has been

shown to be safe and effective in the treatment of vitiligo in both adults and children. According to the FDA, one should avoid use in patients younger than 2 years of age, and only 0.03% tacrolimus is approved for children 2 to 15 years of age.⁴⁰ Given their lack of local side effects and efficacy comparable to topical CSs, they are appropriate for intermittent long-term use and for those who cannot tolerate topical CSs. Face and neck lesions respond best, and occlusion may help with recalcitrant lesions on the extremities. Current limited data suggest that use with phototherapy enhances results. Limiting their application to a small body surface area, such as the face, may alleviate patient and physician concerns about potential systemic absorption.

VITAMIN D3 ANALOGS

Key points

- **As monotherapy, calcipotriene is inferior to topical corticosteroids**
- **Calcipotriene is an effective adjunct to topical corticosteroids**
- **Data do not support the use of calcipotriene with light therapy**

Background

Calcipotriene is a topical vitamin D₃ analog with several different mechanisms of action. While it is used in psoriasis for its antiproliferative effect on keratinocytes,⁴¹ the immunomodulatory effects and enhancement of melanocyte development and melanogenesis are of interest in vitiligo.^{42,43}

Most studies evaluate calcipotriene as adjuvant therapy, but some small clinical trials of calcipotriene monotherapy in children have shown response rates as high as 77% and 78%, with complete repigmentation seen in 16% of patients in one trial and more than 50% repigmentation in 55% of patients in another trial.^{44,45}

Compared to topical CSs, calcipotriene has lower response and repigmentation rates.⁴⁶ However, when combined with CSs, repigmentation rates increase, the delay in the onset of repigmentation shortens, and there is a greater stability of repigmentation compared with either as monotherapy.^{46,47} In addition, combination therapy is effective in some previously steroid nonresponsive patients.⁴⁷ Off-label use of the fixed-combination calcipotriene 0.005% and betamethasone 0.05% topical products once daily is a simple treatment option.

The impact of calcipotriene on light phototherapy has yet to be elucidated. While some studies suggest that there is no benefit of adding calcipotriene to NBUVB phototherapy, and that calcipotriene may actually delay repigmentation,⁴⁸⁻⁵⁰ others report a

reduced number of exposures and lower cumulative irradiation dosage required for repigmentation when added to conventional NBUVB and PUVA phototherapies.^{51,52}

Safety

Topical calcipotriene is considered safe, with only infrequent, mild irritation reported.^{44,45} It should not be used immediately before or after light phototherapy.

Recommendations

Topical vitamin D₃ analogs are safe for use in both children and adults and provide the most benefit when combined with topical CSs. The impact of calcipotriene on light phototherapy is controversial and requires further research.

For the FDA-approved indication of psoriasis, the manufacturer recommends a maximum 100 g weekly of the fixed-combination calcipotriene 0.005% and betamethasone 0.05%, limiting application to less than 30% of the body surface area and not exceeding 4 consecutive weeks of therapy with the ointment (8 weeks for the cream and solution).

PHOTOTHERAPY

Key points

- **Narrowband ultraviolet B light phototherapy is superior to ultraviolet A light phototherapy for the treatment of vitiligo**
- **Phototherapy should be reserved for patients who fail topical therapy**
- **Psoralen plus ultraviolet A light phototherapy may increase the incidence of both melanoma and nonmelanoma skin cancer**

Background

Ultraviolet light has been used to treat patients with vitiligo since the 1800s. The exact mechanism of action is unknown; it is believed to have both immunosuppressive and melanocyte stimulatory effects. In vitro studies have shown that both UVA and UVB phototherapies promote melanocyte migration and proliferation, promote a favorable environment for melanocyte growth, and inhibit autoimmunity.⁵³⁻⁵⁵

Efficacy of UVA

UVA phototherapy is almost always given in conjunction with the photosensitizer psoralen. PUVA phototherapy induces hypertrophy of melanocytes and hyperactive melanosomes (Fig 3).⁵⁶ It also stimulates melanocytes in hair follicles, induces keratinocyte release of factors that simulate melanocyte growth, and may reduce the presence of



Fig 3. Generalized vitiligo on psoralen plus ultraviolet A light phototherapy (**A**) before and (**B**) 1 year into treatment. (Courtesy of Dr Tania Cestari, University of Rio Grande do Sul, HCPA Brazil, Department of Dermatology.)

vitiligo-associated melanocyte antigens on melanocyte membranes.⁵⁷ Clinically, this results in perifollicular repigmentation.⁵⁸

PUVA is approved by the FDA for the treatment of vitiligo,⁵⁹ but high doses of UVA alone (15 J/cm^2) induce repigmentation of more than 60% in half of subjects.⁶⁰ Enhanced with psoralen, response rates are as high as 78% and up to 100% for head and neck lesions in more than half of subjects. Lesions on the extremities are less responsive.^{4,5}

Efficacy of UVB

In the past decade, 311-nm NBUVB phototherapy has superseded PUVA phototherapy in the treatment of vitiligo because it was shown to be clinically more effective. NBUVB induces tyrosinase, an enzyme crucial to melanin production, and increases the presentation of HMB45 on the surface of melanosomes.⁶¹

When used alone, NBUVB phototherapy results in repigmentation rates of 41.6% to 100%.^{48,62-65} Brazzelli et al⁷ found complete repigmentation of 68% of lesions on the face, 57.9% on the neck, and 50% on the trunk. Better results were seen in younger patients.⁷ A similarly powered study found only 9% to have more than 75% repigmentation.⁶⁶ Patients are typically irradiated two to three times a week, with average treatments lasting between 10 weeks and 2 years. In children, an average of 34 treatments was required to achieve 50% repigmentation.⁶³

Compared to PUVA, NBUVB phototherapy produces equivalent^{67,68} or higher rates of repigmentation. Multiple studies have proven that NBUVB phototherapy is superior to PUVA phototherapy in producing disease stability and repigmentation.^{69,70} However, PUVA phototherapy may yield quicker results.^{20,69}

Few reports are available that have recorded the long-term efficacy of vitiligo therapies. The majority of the patients retain PUVA-induced repigmentation for many years, especially when treated until stagnation of repigmentation occurred.⁷¹ Another study, however, reported a reoccurrence of vitiligo in 40% of the patients after finishing PUVA treatment.⁷² For UVB phototherapy and other photochemotherapy regimens, sufficient data are not available to allow critical evaluation of long-term efficacy.

Safety

The regular maintenance and calibration of phototherapy units is crucial to ensure proper dose delivery. Dosimetry is more demanding than with other indications because of the increased photosensitivity of vitiliginous skin. The initial treatment phase is most critical, because UVB-induced conditioning subsequently reduces sensitivity. It is important to control the output of the irradiation units on a regular basis and to keep careful records of the applied doses, not just the exposure times. Missed

treatments require adjusting the dose. A good rule of thumb is to decrease the dose by 25% for every week of time missed; if 4 weeks were missed, start over at base dose.

Common adverse effects in patients receiving PUVA phototherapy include erythema, pruritis, nausea, and headache.⁷³ Mild transaminitis, hypertrichosis, actinic keratoses, and lentigines are less frequent.^{4,5,74} Second-degree burns occurred in patients who received incorrect irradiation doses or sunbathed after using psoralen.⁷⁵ Patients should be instructed to practice extreme sun protection for 24 hours after ingesting or applying psoralens to prevent compounding the therapeutic effect of phototherapy with additional natural UV light. PUVA phototherapy carries a slightly increased risk for both nonmelanoma skin cancer and melanoma.⁷⁶⁻⁷⁸ One large cohort study found that 15 years after the first treatment, there is approximately a fivefold increase in the incidence of melanoma.⁷⁹ A retrospective review reported the incidence for basal cell carcinoma of 0.69%, slightly higher than in age- and sex-matched controls.⁸⁰ Long-term treatment of vitiligo with PUVA phototherapy may induce xerosis, keratoses, "PUVA lentigines," and, rarely, hypertrichosis.⁸¹ NBUVB phototherapy may cause itching, burning, erythema, desquamation, transient hyperpigmentation, blistering, ulceration, and xerosis,^{62,66} but there appears to be no increased risk for non-melanoma skin cancer or melanoma.⁸⁰ All phototherapeutic modalities induce premature photoaging of the skin with prolonged use. This may be more of a concern with khellin, L-phenylalanine, and systemic psoralens, because of the higher UVA doses used in these regimens. The maximum recommended lifetime exposure to PUVA should be limited to 1000 J/cm² or 200 treatments. There is no established limit for NBUVB.

LASER THERAPY

Key points

- **The monochromatic excimer laser allows for the targeted treatment of specific lesions and yields better results than conventional light therapy**
- **In contrast to conventional light therapy, monochromatic excimer laser works well for patients with higher Fitzpatrick skin types**
- **Helium neon laser therapy is effective for segmental vitiligo**

Background

Laser therapy for vitiligo is a relatively new treatment that has gained popularity in the last decade.

The mechanism of action is thought to be similar to conventional light therapy, but lasers allow targeted treatment, less total body irradiation, and less impact on healthy skin.

Monochromatic excimer laser (308 nm)

Background. The best studied and most used laser therapy for vitiligo is the monochromatic excimer laser (MEL; Fig 4), a nonablative technology that emits light in the UV range. The specific wavelength depends on the halogen and noble gas source.⁸²

The xenon chloride MEL emits a 308-nm wavelength, very similar to the 311 nm of NBUVB phototherapy and the Bioskin laser (Bioskin Italia, Bologna, Italy). In most clinical trials, the MEL is used one to three times a week for an initial course of 12 weeks. The MEL is approved by the FDA for treating vitiligo.⁴⁰

Efficacy. When used as monotherapy, repigmentation rates of more than 75% are seen in 16.6% to 52.8% of patients; response rates are as high as 95%.⁸³⁻⁸⁶ On average, it takes 11 to 22 sessions to see repigmentation, more in poorly responsive acral areas.^{87,88} The onset of repigmentation negatively correlates with the total number of treatments.^{83,89} Most cases are stable at 1 year of follow-up.^{88,89} The face and neck respond better than the hands and feet with less total irradiation.^{85-88,90} In contrast to conventional light therapy, higher Fitzpatrick skin types achieve better results.^{86,87} Age, skin type, duration, and evolution of vitiligo do not confound treatment outcomes.⁸⁵ Even some previously NBUVB phototherapy nonresponders achieved repigmentation with MEL.⁸⁴

Compared to NBUVB phototherapy, MEL has better clinical outcomes.⁹¹ Casacci et al⁹² found excellent repigmentation rates in 37.7% of laser treated lesions compared to only 6% with NBUVB phototherapy.⁹²

MEL results improve when used with other modalities. With topical hydrocortisone, 42.8% of patients achieved more than 75% repigmentation compared to only 16.6% using 308-nm MEL alone.⁹³ Topical tacrolimus has similar additive effects.³⁷ The benefit of combining MEL 300-nm with topical vitamin D₃ analogs is less clear; while topical tacalcitol may induce earlier repigmentation, requiring less cumulative irradiation, it may not effect final repigmentation.^{94,95} There are few studies with topical photosensitizers, but the addition of khellin to MEL 308-nm therapy did not provide additional benefit.⁹⁶

Safety. Self-limited erythema and pruritus have been observed (Fig 5).⁸⁴ Missed treatments require adjusting the dose per the manufacturer's protocol to

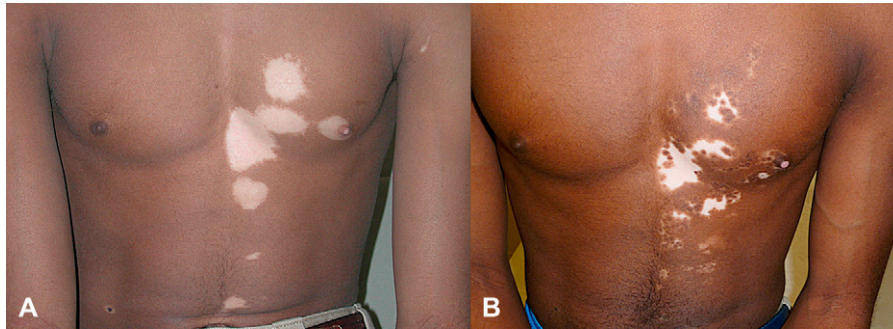


Fig 4. An African American patient on thrice weekly excimer laser therapy (**A**) before and (**B**) 23 months into treatment. (Courtesy of Dr Sarah Stein, The University of Chicago, Section of Dermatology.)



Fig 5. Erythema is a possible side effect in patients receiving excimer laser therapy. (Courtesy of Dr Sarah Stein, The University of Chicago, Section of Dermatology.)

avoid local side effects. Because of the absence of photosensitizing substances and drug-induced toxicity, patients who work outdoors, pregnant women, and patients with liver or kidney failure can also be treated. Furthermore, the short time required for sessions, duration of cycles, and selective exposure of affected skin are significant benefits in terms of safety and efficacy.

Bioskin

Background. A new device out of Italy, Bioskin, transmits focused 311-nm UVB phototherapy (microphototherapy). The goal is to improve cosmesis, reduce adverse effects, and decrease the premature aging and risk of skin cancer associated with total body irradiation.

Efficacy. A large study of 458 subjects compared Bioskin to several other conventional topical therapies. Alone, Bioskin had repigmentation rates of more than 75% in 72% of patients. In combination, the best results were seen with betamethasone dipropionate (>75% repigmentation in 90.2% of subjects). All other tested modalities had improved

repigmentation rates when used in combination with Bioskin compared to use as monotherapy.⁹⁷ While it is a new device and not currently widely available, these promising findings warrant further research.

Helium neon laser

Background. The 632.8-nm helium neon (HeNe) laser is used in patients with segmental vitiligo (SV) who typically have poorer responses to conventional treatment compared to NSV. The dermatomal distribution implies a neural dysregulation, making it slightly different to treat than NSV. The He-Ne laser modifies adrenergic dysregulation of cutaneous blood flow seen in SV⁹⁸ and promotes melanogenesis, melanocyte growth, migration, and survival in the skin.^{99,100}

Efficacy. The He-Ne laser has induced more than 50% repigmentation in 60% of patients with head and neck SV. On average, repigmentation begins after 16 to 17 treatments.^{98,100}

PHOTOCHEMOTHERAPY

Key points

- **Psoralens and khellin enhance the effect of light (natural or artificial ultraviolet A light) phototherapy**
- **L-phenylalanine is an alternative photosensitizer for topical and/or oral supplementation of natural or artificial ultraviolet A light phototherapy**

Background

Throughout history, chemicals were applied to enhance the effects of light therapy for vitiligo.

Psoralens

Background. The furocoumarin psoralens 8-methoxypsoralen (8-MOP; Fig 2), 5-methoxypsoralen (5-MOP), and trimethylpsoralen (TMP) have been successfully used.

Photochemotherapy with topical 8-MOP can be used in patients with small lesions (<5% body surface area) or who are younger than 12 years of age in whom systemic PUVA phototherapy is contraindicated. This therapy must only be performed in an office setting because of the risk of severe phototoxicity. Concentrations of 0.1% 8-MOP or less in alcoholic solutions or ointments are recommended. The frequency of treatment is one to three times per week. Twenty to 30 minutes after application of an even layer, the skin is exposed to UVA radiation, initially at 0.25 to 0.5 J/cm². Two to three times a week exposure time is increased in small steps (15-30 seconds) up to a maximum of 10 minutes. Then, a marginally higher strength of topical psoralen preparation is prescribed and the same time intervals followed. This procedure is repeated until a dosage and exposure time are attained that produce erythema but not burning. The patients need to wash off the remaining 8-MOP with soap and water immediately after the irradiation and apply UVA sunblock to avoid additional environmental UVA exposure.⁸¹

Efficacy. Adisen et al¹⁰¹ found no significant difference in the number of treatments, response rates, and mean cumulative UVA doses of topical PUVA compared with oral PUVA in patients with vitiligo, contradicting previous studies where topical PUVA was inferior to systemic PUVA.¹⁰²

Safety. Topical psoralens are highly phototoxic even at very low concentrations. Pruritus, erythema, edema, blisters, and skin necrosis with massive overdose have all been reported.

Khellin

Background. Khellin is an organic compound with vasodilatory effects. Although the mechanism by which khellin enhances the effect of light remains elusive, an in vitro study of normal human melanocytes suggests a stimulatory effect on melanogenesis and melanocyte proliferation when combined with UVA light.¹⁰³

Efficacy. Khellin can be administered topically or orally. A left-right placebo controlled study of topical khellin with natural sunlight found no benefit over placebo.¹⁰⁴ However, when taken orally in combination with natural light exposure, 16% of patients achieved repigmentation of more than 90%, with a response rate of more than 75%, while controls showed none.¹⁰⁵ Other studies showed repigmentation rates of 70% or more in 41% of patients, a response comparable to treatment with psoralens.^{106,107} Compared directly to PUVA, khellin plus UVA light (Kuva) phototherapy required higher doses and a longer duration of treatment to

achieve the same response, but patients experienced fewer side effects than with PUVA phototherapy. A single open prospective study suggested no additional benefit of adding topical khellin to MEL therapy.⁹⁶

Safety. Khellin rarely causes nausea or mild transaminitis, and in one report it uncovered a case of hereditary porphyria cutanea tarda.¹⁰⁶⁻¹⁰⁸ A study evaluating the long-term side effects of Kuva reported no actinic damage or skin cancer at an average of 40 months of follow-up.¹⁰⁶

L-Phenylalanine

Background. Phenylalanine is an essential amino acid that is critical in initiating melanogenesis in melanocytes. Patients with vitiligo have decreased calcium dependent melanocyte uptake of L-phenylalanine (L-phe).¹⁰⁹ In vitro, oral L-phe with UVA light phototherapy decreased Langerhans cells counts in lesional skin.¹¹⁰ While not a classic photosensitizer, the enzyme that converts phenylalanine has increased activity after being exposed to UVB irradiation.⁶²

Efficacy. L-phenylalanine can be applied topically or taken orally. Most studies evaluate the efficacy of L-phe in combination with light therapy, although Lotti et al⁹⁷ found that 29.3% of patients applying topical L-phe as monotherapy had more than 75% repigmentation. L-phe with UVA light (PAUVA) phototherapy yields better results. The response rates for oral L-phe are up to 81% using sunlight alone (in the Caribbean),¹¹¹ while repigmentation rates vary between 50% and 100%.¹¹²⁻¹¹⁴ Adding topical L-phe to oral L-phe and light therapy is even more beneficial.^{115,116} Facial lesions respond best.^{115,117}

Safety. L-phenylalanine has few significant side effects.^{112,116-118}

Recommendations. Treatment of vitiligo with L-phe appears to be safe and can be used for any patient with access to natural or UVA light. Patients with less than 25% body surface area affected, a disease onset before 21 years of age, and with generalized, symmetrical lesions respond best.¹¹⁸

ANTIOXIDANTS

Key points

- **Topical and oral antioxidants may have a role in protecting melanocytes from destruction by reactive oxygen species**
- **Vitamin E, vitamin C, alphalipoic acid, ginkgo biloba, topical catalase, superoxide dismutase, and polypodium leucotomos have been used in vitiligo**

Dietary supplementation

Background. Oxidative stress has recently been implicated in the pathogenesis of vitiligo. Methionine sulfoxide reductase (MSR), an important reducing agent in repairing damage caused by reactive oxidative species, is less active and present in lower amounts in patients with vitiligo. Lower MSR increases melanocyte sensitivity to oxidative stress and ultimately leads to greater cell death.¹¹⁹ Oral antioxidant therapy results in elevated catalase activity and a decrease in reactive oxygen species.¹²⁰

Efficacy. The role of antioxidant supplementation in treating vitiligo has yet to be defined. Studies suggest it is an effective, inexpensive, well tolerated treatment. Combining oral and topical phenylalanine provides better results than either as monotherapy.¹²¹ In a double-blind, placebo-controlled trial, monotherapy with oral ginkgo biloba significantly decreased disease progression compared to placebo.¹²²

DellAnna et al¹²⁰ revealed that supplementing NBUBV phototherapy with a combination of alpha lipoic acid, vitamin C, vitamin E, and polyunsaturated fatty acids improved repigmentation rates from 18% to 47%. Similar results were seen in patients treated with oral vitamin E and NBUBV,¹²³ but not with PUVA.¹²⁴

Catalase and superoxide dismutase

Background. Catalase and superoxide dismutase are enzymes with antioxidant properties. They are available in a combination topical medication marketed outside of North America as Vitix (Crawford Pharmaceuticals, Knutsford, UK).

Efficacy. While one case study showed remarkable repigmentation response on the face and hands of patients using combination topical pseudocatalase/calcium with short-term UVB phototherapy,¹²⁵ other studies show no such benefit.^{126,127} In patients undergoing Dead Sea climatotherapy (where the mineral content of the water and ozone composition allow maximum natural UV light exposure without phototoxicity), topical pseudocatalase was shown to initiate repigmentation after just 10 to 16 days, compared to the 5 to 14 weeks in those using either as monotherapy.¹²⁸ One study suggested that topical catalase/superoxide dismutase may be as effective as topical 0.05% betamethasone.¹²⁹

Polypodium leucotomos

Background. Polypodium leucotomos (PL) is a fern found in the American subtropics. The extract has antioxidant, immunomodulating, and photoprotective qualities and is used to treat a variety of

ailments ranging from bronchitis to Alzheimer disease.¹³⁰

Efficacy. Adding 250 mg of oral PL extract to conventional NBUBV phototherapy significantly improves repigmentation from 27% to 44% on the head and neck.¹³¹ In healthy subjects without vitiligo, oral PL reduces the cutaneous phototoxicity of PUVA and UVB phototherapies.¹³⁰

Safety. The safety profiles of many oral and topical antioxidants are unknown, even more so when used in combination with other modalities. Topical catalase/superoxide dismutase causes transient erythema, pruritis, and peeling.^{127,129,132}

Recommendations. There is good evidence supporting oral antioxidant supplementation of conventional therapy, specifically NBUBV phototherapy. It is also likely a safe, widely available, and inexpensive adjunct. However, defining dosing parameters, efficacy, and side effect profiles require additional research.

SURGICAL THERAPY

Key points

- **Surgical treatment for vitiligo is invasive and not without risks; however, it can be an excellent option for patients who fail non-surgical therapy**
- **Patients with Koebner phenomenon could worsen with surgical treatment**
- **Melanocyte transplant techniques include suction blister grafting, split-thickness grafting, punch grafting, and melanocyte suspension**
- **Adverse outcomes include scarring, graft failure, koebnerization, infection, cobblestoning, and variegated pigmentation**

Background

Surgical treatment is an excellent option for patients who are unable to achieve cosmetically pleasing results with nonsurgical methods. It should be reserved for stable recalcitrant lesions. Special care must be taken to evaluate for koebnerization, which could worsen their disease after the surgery. Surgical treatment can essentially be broken down into two main categories: grafting melanocyte-rich tissue and grafting melanocyte cell suspensions.

Blister graft

Background. The blister graft (BG) technique is used to create donor epidermal graft tissue. This technique creates a subepidermal bulla at the donor site, from which the roof is surgically removed and transplanted onto the recipient site. While techniques vary, inducing the bulla is usually accomplished by applying a cup or syringe under constant

negative pressure. Tang et al¹³³ describe in detail a technique that can be easily performed in the outpatient setting. Local phototoxicity has also been used to raise donor bullae.¹³⁴ Grafts can be harvested from various sites, but the flexor aspect of the arm appears to most reliably produce a bulla.¹³⁵ The bulla is then “unroofed” and transplanted onto the recipient site, which must be prepared to enable proper adherence and uptake of the graft. This is performed using the suction blister technique,¹³³ laser ablation,¹³⁶ or other means of creating a dermabraded surface. The graft is then cut to the appropriate size and shape and transferred to the recipient site. For larger lesions, multiple grafts can be placed adjacent to one another.¹³⁷ Repigmentation spreads outward from the graft.

Efficacy. The cosmetic response to suction blister grafting is very good and has even been shown to improve leukotrichia in some patients.¹³⁸ Complete repigmentation occurs in as many as 90% of patients.¹³⁹ In a clinical study of 45 patients with SV or NSV, reepithelialization occurred in an average of 2 weeks, and the skin color of the grafted area normalized in approximately 6 months. Most patients with SV retained the pigment, but there was some loss of pigmentation in the patients with NSV.¹³⁴ Failure to repigment may be caused by a Koebner response.¹⁴⁰ Hatchome et al¹⁴⁰ found pigment from the graft had a two- to threefold expansion to surrounding tissues after 3 to 4 months in most patients. Adding light therapy may enhance repigmentation.^{141,142}

Split-thickness skin graft

Background. The split-thickness skin graft (STSG), though less popular than the BG, can be used to successfully treat stable, recalcitrant vitiligo. The major advantage is its ability to cover large areas with a single surgical procedure. The graft is harvested with the assistance of a dermatome, which creates a graft of uniform thickness. Grafts are usually harvested from hidden areas, because the donor site may heal with abnormal pigmentation and texture. It is then meshed to prevent seroma formation and to cover a greater surface area, placed over a dermabraded recipient site, and dressed in gauze.¹⁴³

Efficacy. Agrawal et al¹⁴⁴ treated 32 sites in 21 patients with stable refractory vitiligo using this technique. Sixty-eight percent of patches responded with 100% repigmentation; the remainder achieved 90 to 95% repigmentation. It took an average 6.3 months to achieve close to a full color match.

Compared to BG, the STSG can cover a larger surface area. While no large studies have been performed, Ozdemir et al¹⁴⁵ had the STSG result in

higher percent repigmentation than the suction BG in a single patient. Repigmentation is greater in patients treated with chemophototherapy plus STSG versus punch grafts (PGs), with repigmentation rates of more than 75% in 83% of patients with STSGs versus 44.1% with PGs.¹⁴⁶

This procedure, however, requires the use of anesthesia and can leave harvest sites cosmetically displeasing, whereas the BG can be performed in the office and the donor site is often left unscathed.

Punch graft

Background. Punch grafting, or minipunch grafting, is one of the most commonly used techniques. Multiple tiny PGs are harvested and placed onto the recipient site that was either dermabraded or perforated with a similar size punch.¹⁴⁷ Boersma et al¹⁴⁸ describe this technique in detail. Similar to other types of grafting, repigmentation spreads peripherally from the implant.

Efficacy. Punch grafting can provide good repigmentation and cosmetic results. In one of the largest clinical studies, performed in 1000 patients with vitiligo, Malakar et al¹⁴⁹ evaluated this technique. They reported 90% to 100% repigmentation in 74.5% of patients, no repigmentation in 10.5%, and depigmentation of the grafts in 2.3%. In a smaller study, 13 patients had erbium-doped yttrium aluminium garnet laser ablation of the recipient site with repigmentation in 92%.¹⁵⁰

The addition of light therapy may provide additional benefit. PG and NBUVB phototherapy appear to provide better repigmentation, with success in 86.36% after just one postsurgical exposure to NBUVB light phototherapy. Average pigment spread for this group was 6.5 mm, whereas patients treated with PG and PUVA averaged 6.38 mm.^{151,152} The addition of topical fluocinolone in patients receiving PG and PUVA phototherapy did not enhance the results.¹⁵²

Autologous melanocyte suspension transplant

Background. The essence of the autologous melanocyte suspension transplant (AMST) is to harvest tissue from a donor site (PG, BG, curettage, or STSG), release individual cells into a suspension, and then transplant them onto deepithelialized recipient skin.¹⁵³ Some techniques transplant both keratinocytes and melanocytes, others just melanocytes. Cell culturing has also been used to increase the number of viable cells for transplant using less donor tissue.

Efficacy. Cosmetic results achieved using AMST are very promising (Fig 6); there is more than 70% repigmentation in 77% of grafted lesions and 0% using placebo.¹⁵⁴ In a large (n = 142) long-term study



Fig 6. This female patient with generalized vitiligo received one melanocyte–keratinocyte transplantation procedure to the area. The after pictures are 6 months postprocedure. (Courtesy of Dr Iltefat Hamzavi and Dr Marsha Henderson, Henry Ford Hospital, Department of Dermatology.)

of efficacy of noncultured melanocyte–keratinocyte cell transplantation in patients with stable vitiligo vulgaris, Mulekar¹⁵⁵ found that 56% of patients achieved repigmentation rates of more than 95%, maintained at 6 years of follow-up. In stark contrast to nonsurgical methods of treatment, lesions on the ankles, legs, joints, and fingers had the best response to therapy, while lesions on the face responded poorly. This technique may be more efficacious in patients with SV than focal vitiligo, because 84% and 73% of patients had more than 95% repigmentation, respectively.¹⁵⁶ Similar results were achieved in SV treated by cultured AMST.¹⁵⁷ When comparing noncultured versus cultured melanocyte suspension transplant, noncultured transplants may achieve similar or slightly better repigmentation.¹⁵³ Few studies have tested whether phototherapy enhances results; a response was seen in 75% of patients with focal or SV and 30% of patients with generalized vitiligo treated with NB-UVB phototherapy 3 weeks postoperatively.¹⁵⁸ These surgical techniques improve both physical results and quality of life, as assessed by the Dermatology Life Quality Index scoring questionnaire.¹⁵⁹

Safety. Side effects with any skin surgery include scarring, infection, and hyperpigmentation.^{146,152} In patients who koebnerize, depigmentation can occur at both donor and recipient sites. With suction BG, one study found that only patients with generalized vitiligo experienced koebnerization of donor sites, and all failed to repigment.¹⁴⁰

With STSG, the risk of graft failure is often minimal, but patients should be forewarned.^{144,146} Achromatic fissuring, contracture, tire pattern appearance, and milium formation have all been reported in patients after STSG.¹⁴⁶

The most common adverse effect of PG is development of a cobblestoned texture, with the grafts raised in comparison to the surrounding skin.^{146,151,152} The use of silicone gel dressings may prevent graft

lifting.¹⁶⁰ A variegated or polka dot appearance of repigmented skin and color mismatch are also possible.^{146,149} While very little has been reported for AMST, infection, scarring, graft failure, koebnerization, and irregular pigmentation are theoretically possible.

Recommendations. Surgical treatment should be reserved for patients with stable vitiligo refractory to nonsurgical therapy. In the appropriate candidate, the results can be both excellent and long-lasting. Both the BG and PG technique are advantageous because they can be performed without general anesthesia and often leave the donor site unscathed. The STSG can be useful to cover large areas, but yields less desirable cosmetic outcomes at the donor site.

AMST is a great alternative to tissue grafting; however, preparation of the suspension is complex and time-consuming. This technique appears to work best in patients with focal or SV, and can provide excellent results in traditionally difficult to treat locations. Moreover, larger areas require less donor graft with the use of melanocyte culture techniques.

DEPIGMENTATION

Key points

- **Depigmentation may be beneficial to patients who fail repigmentation therapy or have extensive disease**
- **Topical agents include monobenzone and hydroquinone**
- **The Q-switched ruby laser and the Q-switched alexandrite laser can be used alone or in combination with topical depigmenting agents**

Background

We are still far from being able to achieve complete repigmentation in all patients. When satisfactory results are unattainable, depigmentation therapy may provide more desirable cosmetic outcomes.

Topical agents that depigment normal skin include hydroquinone and monobenzone, which is approved by the FDA for the treatment of vitiligo.⁵⁹ Their mechanism of action is not entirely clear, but studies have shown that both induce melanocyte death.^{161,162}

Efficacy

In a clinical study of patients with severe vitiligo, monobenzone 20% produced depigmentation in 84% of patients, with complete depigmentation in 44%.¹⁶³ In a study with hydroquinone, 69% achieved total depigmentation; however, 36% of those had some repigmentation at 2 months to 3 years of follow-up.¹⁶⁴

The Q-switched ruby laser has been extensively used for depigmentation in vitiligo universalis, although the Q-switched alexandrite laser is also effective.¹⁶⁵ Njoo et al¹⁶⁴ showed that combining hydroquinone and the Q-switched ruby laser results in complete depigmentation in 69% of patients; however, 44% had repigmentation 2 to 18 months posttreatment. Patients with a positive Koebner phenomenon are more likely to achieve stable results.¹⁶⁶

Safety

Both hydroquinone and monobenzone may cause burning, itching, and contact dermatitis.^{163,164,167} Conjunctival melanosis, pingueculae, and corneal pigment deposition have been reported with monobenzone.¹⁶⁸

Recommendations

Topical depigmenting agents and laser therapy provide cosmetic relief, but the effects may not be permanent. Little is known about the optimal frequency and duration of laser therapy.

CAMOUFLAGE

Key points

- Camouflage can create a cosmetically pleasing appearance, and should be recommended to patients at all stages of treatment
- It can be temporary (makeup), semipermanent (self-tanning agents), or permanent (tattoo)
- Camouflage improves patient scores on the Dermatology Quality of Life Index

Cosmetics

Although cosmetic agents have no effect on the disease, they help with the psychosocial burden of vitiligo, especially when extensive or with lesions on the face, head, and neck.¹⁶⁹ A questionnaire study

of patients in a vitiligo self-help group found that 70% of females and 41% of males use camouflage.¹⁷⁰ Camouflage improved scores on the Dermatology Quality of Life Index in a quality of life and stigmatization study after just 1 month. It also improved patient's "feelings of embarrassment and self-consciousness" and "choice of clothing."¹⁶⁹ In children with vitiligo (and other cosmetically disfiguring conditions), camouflage attained satisfactory results.¹⁷¹

Self-tanning agents provide semipermanent camouflage. Dihydroxyacetone (DHA), the active ingredient in most self-tanners, is approved by the FDA for the treatment of vitiligo.⁵⁹ The stain lasts up to 10 days.¹⁷² In 88.9% of patients with vitiligo of their face, hands, or feet, 6% DHA produced moderate to marked satisfaction.¹⁷³ Applying 5% DHA to lesions every other day for 2 weeks led to satisfactory results in 80% of patients.¹⁷⁴ In lighter complexions, lower concentrations of DHA achieve closer color matching.^{172,173}

Makeup can help a great deal to disguise vitiligo lesions. Although fairly limited by its tendency to wear off and the need for multiple applications, the result is immediate. Makeup is somewhat troublesome in vitiligo of the hands because it tends to wear off easily. One patient discovered that by layering makeup, finishing powder, and Caviol spray (a long-lasting waterproof barrier used around stomas and for incontinence) on fingertip lesions allowed her to go all day without reapplying.¹⁷⁵

Tattoo

Permanent dermal micropigmentation, or tattoo, is especially helpful for mucosal lesions, which are difficult to cover up or treat with conventional therapy. In a study of 30 patients with localized stable vitiligo who underwent cosmetic tattooing, 76.7% had excellent color matching. The best results were seen with mucosal lesions and in patients with darker complexions.¹⁷⁶ Potential adverse events include koebnerization, allergic reactions to the tattoo pigment, and imperfect color matching.

NEW CONCEPTS IN TREATING VITILIGO

Key points

- Psychotherapy helps with the psychosocial effects of vitiligo, but may also affect disease progression
- Tumor necrosis factor- α inhibitors reportedly alter disease progression of vitiligo, but this has yet to be studied in clinical trials
- A preliminary study suggests that minocycline may halt disease progression
- Immune suppressants may have a role in the treatment of vitiligo

Psychotherapy

Vitiligo can be very distressing because of its chronic course, cosmetic disfigurement, and perceived stigma. Treating psychological manifestations of the disease might not only help patients' overall sense of well-being, but may actually improve clinical outcomes. In a randomized controlled study, Papadopoulos et al¹⁷⁷ found that 1 hour of weekly cognitive behavior therapy and coping skills training profoundly improved quality of life, self-esteem, and perceived body image. In addition, the evaluation of photographs taken pre- and posttreatment suggested that it may affect disease progression. While these results are preliminary and need to be validated, they do support the impact of psychological stress on physical disease.

Tumor necrosis factor- α inhibitors

Although they are currently not indicated for the treatment of vitiligo, preliminary findings suggest that this class of drugs may provide relief in certain patients.

Background

TNF α is a proinflammatory cytokine that can induce melanocyte death and inhibit melanocyte stem cell differentiation. Birol et al¹⁷⁸ revealed that vitiliginous skin has significantly higher levels of TNF α and IL1 α compared to normal skin in the same patient.

Efficacy

No studies have been conducted to evaluate the safety or efficacy of TNF α inhibitors in vitiligo, although several case reports suggest they may affect pigmentation. A patient receiving infliximab for ankylosing spondylitis experienced a halt in progression of his vitiligo and repigmentation of some lesions.¹⁷⁹ Several patients taking TNF α inhibitors for psoriasis also experienced improvement of their vitiligo.^{137,180,181} Additional research is needed to determine if TNF α inhibitors have a role in treating patients with vitiligo.

Minocycline

Minocycline has antibiotic, antiinflammatory, immunomodulatory, and antioxidant properties.¹⁸² A recent study found that daily minocycline can halt progression of vitiligo during and after therapy.¹⁸² While promising, additional controlled studies are warranted to assess the role of minocycline in treating vitiligo.

Systemic immunosuppressants

Immune suppression has a clear role in treating vitiligo. However, aside from CSs, there is very little in the literature about the use of systemic immunosuppressants. This lack of data is likely related to the high-risk side effect profile. Still, their use deserves academic mention. In one randomized controlled study, azathioprine increased the benefits of PUVA phototherapy in vitiligo.¹⁸³ Cyclophosphamide, when given in pulse therapy with dexamethasone for the treatment of pemphigus vulgaris, induced repigmentation in a patient with vitiligo universalis that had previously been recalcitrant to systemic steroids.¹⁸⁴ Chicken models suggested a role for cyclosporine in treating vitiligo¹⁸⁵; however, only one of six human subjects showed even minimal to moderate improvement when treated with 6 mg/kg/day.¹⁸⁶

COST

Key points

- **Vitiligo is a lifelong disease that can become expensive to treat both for the patient and the health care system**
- **Treatment should start with less aggressive, cost effective modalities, reserving more invasive and expensive options for those who fail first-line therapy**

The cost and accessibility of therapy must be considered when choosing a treatment plan for this chronic, often lifelong disease, especially for patients with financial limitations or those who live in rural or underdeveloped areas. A physician in Bangladesh who cared for patients with minimal monetary resources treated them effectively for \$3 to \$6 per month with topical psoralen, natural sunlight, topical steroids, multivitamins, and oral levamisole (this drug was later found to be ineffective and was withdrawn from the US market because of serious side effects).^{187,188} There is continued need for an inexpensive treatment regimen that can be self-administered by patients with financial or practical obstacles.

Topical therapy is generally the least expensive treatment modality. Generic topical CSs are \$10 to \$30 per tube (15-30 g), whereas topical CIs can exceed \$100 for 30 g.¹⁸⁹ Vitamin D₃ analogs cost upwards of \$160 for 60 ccs of 0.005% solution.¹⁹⁰

The cost of phototherapy is difficult to pin down because the overhead is highly dependent on the institution. In 2004, a teaching hospital in Ireland found that the average annual cost of NB-UVB phototherapy for psoriasis was 325 € (~\$400) per person.¹⁹¹ The purchase price of an excimer laser

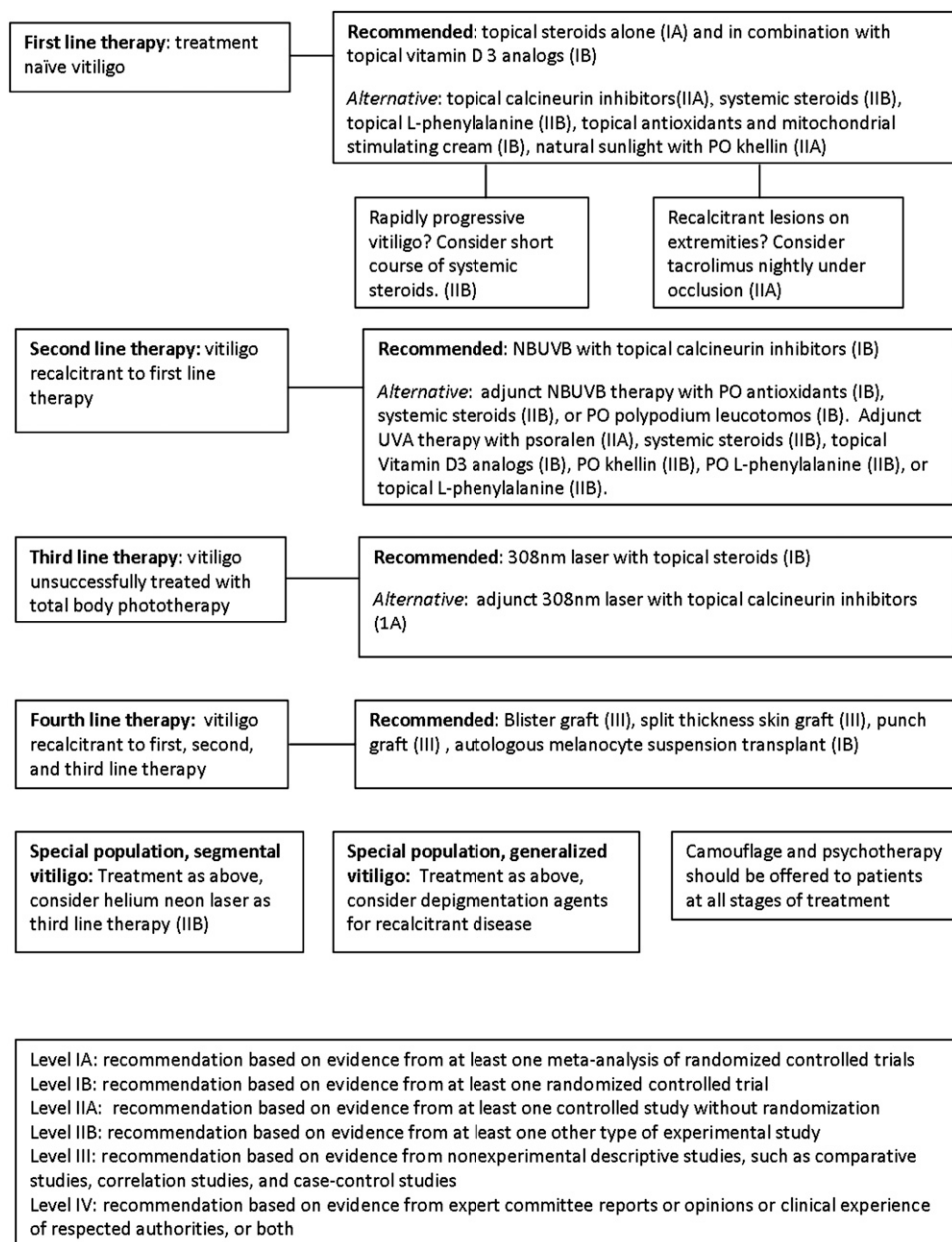


Fig 7. An approach to treating a patient with vitiligo (treatment algorithm): we have divided treatment options into first-, second-, third-, and fourth-line options. The treatment order was determined by the level of evidence in the literature for each treatment. Treatment options for special populations are also included.

is \$85,000 to \$90,000 plus operational and maintenance costs.¹⁹²

The expense of surgically treating vitiligo depends on methodology, overhead charges, the surface area being treated, and use of anesthesia. Worldwide, it can range from \$1500 to \$10,000.

Treatment algorithm

Choosing a treatment for vitiligo can be overwhelming. In general, first-line therapy should be

safe, effective, minimally invasive, and cost efficient. More complex, invasive, and time-consuming options should be reserved for patients with recalcitrant disease (Fig 7). Each therapeutic modality should be tried for a sufficient period of time as initiation of pigmentation varies and is in general rather slow. An effective therapy should be continued as long as there is improvement or the lesions completely repigment. We are in need of data on maintenance regimens or the long-term persistence of

pigmentation with any of the recommended therapies. It is the practice of the senior author to stop treatment and follow-up as necessary if new lesions or symptoms of associated diseases occur.

First-line. There are many topical and some oral agents that are inexpensive, easy to administer, and effective at halting disease progression and inducing repigmentation. CSs are consistently reported as the single most effective topical agent, with CIs being a close second. Because local side effects of CSs are possible, scheduled drug holidays are recommended.

Topical CIs are effective as monotherapy in patients who do not tolerate topical CSs. They are also effective for recalcitrant lesions on the extremities when applied nightly under occlusion. Current data does not support monotherapy with topical vitamin D₃ analogs, but they can augment the effect of topical steroids even in previously steroid nonresponsive patients. Topical L-phenylalanine, topical antioxidants and mitochondrial stimulating cream, and natural sunlight with oral khellin have all been suggested as efficacious alternative first-line therapies.

When administered in patients with active disease, a short course of oral or intravenous steroids can arrest progression and induce repigmentation in the majority of patients. However, the optimal dose to maximize benefits and reduce the incidence of side effects has yet to be determined.

Second-line. Given the cost, time commitment required by patients and staff, and higher incidence of side effects, phototherapy is recommended as second-line therapy for patients who fail conservative first-line treatment(s). NBUVB phototherapy produces the greatest clinical improvement compared to other forms of light therapy; combinations with topical therapy work better than either alone. Topical CIs with NBUVB phototherapy have the best clinical outcomes compared to other topical adjuvant therapy. It is uncertain whether adding a vitamin D₃ analog to NBUVB phototherapy enhances the effects. While inferior to NBUVB in terms of clinical response, both UVA and broadband UVB phototherapies with various adjuvant therapies are beneficial as alternative second-line treatments.

Third-line. Targeted phototherapy with the 308-nm MEL is effective as monotherapy, and superior to NBUVB phototherapy when compared side by side. However, it should be reserved for patients who fail NBUVB phototherapy, except in very limited disease, or in patients who can afford the time and cost of therapy. MEL works best in combination with topical CSs or CIs.

Fourth-line. Surgery should be offered when lesions persist despite appropriate therapy. While the specific technique will depend on individual

patient characteristics and the custom practice of the surgeon, it can provide excellent cosmetic results for lesions recalcitrant to other modalities.

Special populations

Although patients with SV have been studied alongside those with NSV, it is unclear how applicable study results are to this population. SV tends to be more stable and recalcitrant to treatment. The He-Ne laser works via different mechanisms more targeted to the disease process of SV, and is more effective in this population. Generalized/universal vitiligo may also require tailored treatment. The extent of disease can be so great that it may be nearly impossible to provide cosmetically pleasing repigmentation. For these patients, depigmenting agents should be offered.

Considerations

At all stages of therapy, keep in mind that vitiligo can be a lifelong disease that may extensively damage one's psychosocial sense of well-being. Acknowledging this hidden impact of disease on quality of life and offering support for dealing with it will greatly improve the physician–patient relationship and promote a positive connection. Camouflage can provide temporary cosmetic relief, and psychotherapy should be offered to help patients deal with the psychological disease burden.

Future research

Additional advances will require an accepted standardized tool for evaluating disease severity and response to therapy. Currently, it is impossible to merge data from numerous small trials and many different investigators, and to synthesize it to draw conclusions or make recommendations for treatment.

In response to this obstacle, the Vitiligo European Task Force proposed a system to standardize evaluation of disease severity by looking at extent of disease, stage of disease, and disease progression. These parameters are used to calculate a Vitiligo Assessment Severity Index, which is measurable against anyone else evaluated by this method.¹⁹³ Implementing a standardized method will enable future investigators to conduct more meaningful metaanalyses, resulting in more accurate recommendations to clinicians.

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