

Consensus on the Diagnosis and Treatment of Vitiligo in China (2021 Revision)[#]

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Abstract

Vitiligo is a common depigmented skin disease that negatively affects the physical and mental health of patients. The 2018 version of the Vitiligo Treatment Consensus has been updated based on the research progress on vitiligo in the past 3 years in combination with the clinical experiences of experts. The newly revised points include maintenance therapy, early glucocorticoid intervention, and oral mini-pulsed glucocorticoid administration protocols. The prospect of using JAK inhibitors in the treatment of vitiligo is also discussed.

Keywords: vitiligo, therapy, glucocorticoids, phototherapy, calcineurin inhibitor, expert consensus

Introduction

The consensus on the treatment of vitiligo in China (2021 revision) is a revision of the previously published version (2018),¹ and integrates recent research on vitiligo, clinical

experience in the last 3 years, and the panel discussion of experts from the vitiligo groups of the Chinese Society of Integrated Chinese and Western Medicine, the Vitiligo Research Center of the Chinese Society of Dermatology, and the Pigmentary Disorder Group of the Chinese Dermatologist Association. The newly revised points include (1) the addition of maintenance therapy in vitiligo treatment, which prevents the repigmented lesions from undergoing re-depigmentation; (2) early intervention with and oral mini-pulsed administration of systemic glucocorticoids; and (3) promising treatment options using systemic and topical JAK inhibitors.

The overall goal of vitiligo treatment is to halt disease progression, induce repigmentation by stimulating melanocyte differentiation and proliferation, and use maintenance therapy to prevent depigmentation of repigmented lesions.

Major concerns regarding treatment options

Phases of vitiligo

Vitiligo usually has an active phase and an inactive/stable phase. The assessment of active vitiligo mainly relies on

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the vitiligo disease activity (VIDA) score,² characteristic skin manifestations, the Koebner phenomenon, and Wood lamp findings.

VIDA score

Patients are assigned +4 points if new skin lesions have appeared or previous skin lesions have enlarged over the past 6 weeks, +3 points if new skin lesions have appeared or previous skin lesions have enlarged over the past 3 months, +2 points if new skin lesions have appeared or previous skin lesions have enlarged over the past 6 months, +1 point if new skin lesions have appeared or previous skin lesions have enlarged in the past 1 year, 0 points if lesions have been stable for at least 1 year, and -1 point if lesions have been stable for at least 1 year and are spontaneously repigmenting. A total VIDA score of >1 point indicates that the disease is in the progressive stage, while a score of ≥4 points indicates that the disease is in the rapidly progressive stage.²

Characteristic skin manifestations

The clinical indications of disease activity are hypo- or depigmentary lesions with poorly defined borders, inflammatory vitiligo (eg, hypochromic macules with an inflamed and erythematous border or mild pruritus), trichrome vitiligo, and confetti-like hypopigmentation.³

Koebner phenomenon (isomorphic reaction)

The Koebner phenomenon is the occurrence of new skin lesions within 1 year at the site of skin trauma (such as excision, scratch, friction, pressure ulcer, thermal burn, frostbite, and chemical corrosion), inflammatory skin conditions (such as allergic contact dermatitis and tattooing), and iatrogenic skin injuries (such as vaccine inoculation, radiotherapy, and phototherapy).

Wood lamp findings

Wood lamp examination reveals porcelain-white macules with an ill-defined border. The hypochromic areas are larger when examined under a Wood lamp than under daylight conditions.

The diagnosis of active vitiligo is made if the affected individual has one of the abovementioned criteria. Stable vitiligo shows negative results, including (1) a VIDA score of 0, (2) hypochromic lesions with a sharp or hyperpigmentary border, (3) absence of the Koebner phenomenon, or (4) hypochromic areas that are smaller when visualized using a Wood lamp than under daylight conditions. Reflectance confocal microscopy⁴ and dermoscopy are also widely used in the diagnosis of vitiligo.

Severity of vitiligo

The vitiligo severity is classified into four grades based on the area of the depigmented skin. Vitiligo classified as grade 1 (mild) when less than 1% of the body surface area (BSA) is affected, grade 2 (moderate) when 1%–5% of the

BSA is affected, grade 3 (moderate-to-severe) when 6%–50% of the BSA is affected, and grade 4 (severe) when more than 50% of the BSA is affected. The palm surface area (PSA) is commonly used to estimate the depigmented area of vitiligo; a patient's PSA represents 1% of their BSA. For affected areas of less than 1% of the BSA (1 PSA unit), the knuckle unit of the fingers can also be used for area assessment. One PSA relative to 18 knuckle units accounts for 0.54% of the BSA, so a knuckle unit represents 0.03% of the BSA.⁵ The vitiligo area scoring index (VASI) is determined based on the PSA units. The total body VASI is calculated using the following formula by considering the contributions of all body regions (possible range 0–100).⁶
$$VASI = \sum [PSA \text{ units}] \times [\text{residual depigmentation}]$$
 Vitiligo area can also be determined using the scoring sheet vitiligo extent score, which is available online at www.vitiligo-calculator.com.⁷

Types of vitiligo

According to the Vitiligo Global Issues Consensus Conference (2012) and expert panel discussion, vitiligo can be further classified as segmental, non-segmental, mixed, and unclassified.⁸

Segmental vitiligo (SV)

SV is characterized by the distribution of depigmented macules within certain dermatomes in a unilateral and asymmetric pattern, partially or totally matching a dermatome. Few cases have bilateral or pluri-segmental distribution.

Non-segmental vitiligo (NSV)

NSV is also known as vitiligo vulgaris, and is further divided into sporadic, generalized, acrofacial, neck and facial, and mucosal subtypes. Sporadic vitiligo refers to the presence of depigmented macules in more than two areas, with a severity grade of 1–3. Generalized vitiligo refers to the presence of depigmented macules covering more than 50% of the BSA (grade 4). The acrofacial, neck and facial, and mucosal subtypes tend to develop into generalized vitiligo.

Mixed vitiligo

Mixed vitiligo refers to the concomitant presence of both SV and NSV in the same patient.

Unclassified vitiligo (previously termed focal vitiligo)

Unclassified vitiligo refers to solitary depigmented macules with a severity grade of 1. It is difficult to identify unclassified vitiligo as NSV or SV.

Other factors

To achieve a correct diagnosis, it is also critical to obtain the following information: location of depigmented macules, age of onset, duration of disease, previous

medication history, family history, and presence of other diseases such as autoimmune diseases.

Rules for disease management

Active phase of vitiligo

Unclassified vitiligo

Unclassified vitiligo is treated with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) (such as tacrolimus and pimecrolimus). Topical application of 0.1% 8-methoxypsoralen or other topical preparations containing psoralen and topical vitamin D3 derivatives are also considered. The preferred treatments for unclassified vitiligo are 308 nm excimer laser therapy, monochromatic excimer light (MEL) therapy, and narrowband ultraviolet B (NB-UVB) therapy. Systemic corticosteroids should be administered in cases with rapid progression, as early intervention may arrest spreading vitiligo.

NSV and mixed vitiligo

Systemic corticosteroids are appropriate for patients with active vitiligo with a VIDA score of more than 3. Traditional Chinese medicine (TCM) and Chinese herbs, NB-UVB, 308 nm excimer laser, and MEL can also be considered. The starting dose of these phototherapies should be set at half or one-third of the standard dosage used for routine treatment in patients with rapid disease progression. The co-administration of systemic corticosteroids and antioxidants is likely to prevent vitiligo enlargement potentially induced by phototherapy-triggered oxidative stress. The topical treatments used for NSV and mixed vitiligo are similar to those used for the active phase of unclassified vitiligo.

SV

Surgical treatment is recommended for patients with treatment-resistant and stable SV (no new lesions or expansion of lesions for 6 months or more). Surgical treatments include suction blister autologous epidermal grafting, minigrafting, ultrathin epidermal grafts, and transplantation of autologous epidermal cell suspension or melanocytes. Other treatments for SV are similar to those used for the stable phase of unclassified vitiligo.

Stable phase of vitiligo

Unclassified vitiligo

Topical photosensitizers (methoxsalen, 8-Methoxypsoralen), TCS, TCI, and vitamin D3 analogs are used to treat unclassified vitiligo. Autologous epidermal grafting or transplantation of autologous cultured melanocytes is also recommended. Localized phototherapies for unclassified vitiligo are similar to those used in active vitiligo.

NSV and mixed vitiligo

Phototherapies (such as NB-UVB, 308 nm excimer laser and MEL), TCM and Chinese herbs, autologous epidermal grafting, or autologous melanocyte transplan-

tation are used to treat NSV and mixed vitiligo, with treatment preferably administered at the exposed sites or the regions the patient wishes to treat. Topical medications are prescribed for NSV and mixed vitiligo in accordance with the recommendations for stable unclassified vitiligo.

SV

Autologous epidermal grafting and autologous melanocyte transplantation are also appropriate for patients with stable SV (lesions unchanged for at least 6 months). The usual surgical procedures include suction blister mini-grafting, ultrathin epidermal grafts, and transplantation of autologous cultured epidermal cell suspension. Other therapies for SV are similar to those used for unclassified vitiligo.

Treatment instructions

Use of corticosteroids

Topical application

TCS are effective in treating small-sized lesions (especially those covering less than 3% of the BSA); super-potent (class 1) or potent (class 2–3) corticosteroids should be chosen. For sensitive locations such as the face and the body folds, TCS are used for no longer than 1 month, and are then replaced with TCI, preferably under the guidance of a specialist. Continuous use of TCS is only used for acrofacial vitiligo. High-potency topical fluorinated steroids should be avoided for periocular vitiligo due to potential adverse effects. If there has been no response after 3–4 months of continued treatment, TCS should be changed or used in conjunction with other modalities.

Systemic administration

Early use of systemic corticosteroids is imperative to arrest rapid progression in patients with active vitiligo (VIDA score >3). A low dose of oral prednisone (0.3 mg/kg/d) for 1–3 months may be appropriate in the treatment of adult progressive vitiligo. If no disease progression is noted, the prednisone dose should be tapered by 5 mg every 2–4 weeks until the dose is 5 mg of prednisone on alternate days. Oral prednisone should be prescribed for at least 3 months to achieve a good response. An intramuscular injection of 1 mL of diprospan (containing 2 mg betamethasone sodium phosphate and 5 mg betamethasone dipropionate) can be administered once per month to patients with active vitiligo; however, only one to four injections should be administered before patients are referred to a specialist. Oral mini-pulse therapy reportedly achieves stronger beneficial effects and fewer adverse effects than daily administration of systemic corticosteroids. Examples of mini-pulse therapy include oral dexamethasone (2.5 mg/d)¹⁰ or methylprednisone (0.5 mg/kg)¹¹ on 2 consecutive days per week for 3–6 months. Other immunosuppressants may be considered for patients with contraindications to steroids.

Use of phototherapies

Localized phototherapy

NB-UVB therapy is administered two to three times per week. The starting dose setting of phototherapy depends primarily on the anatomic site being treated and the minimum erythema dose (MED), which is determined by initial photo-testing of depigmented skin before phototherapy. The patients are initially treated with 70% of the MED; subsequent doses are adjusted contingent upon the presence of a visible erythema reaction at the treated sites. If the erythema reaction is barely visible or lasts for less than 24 hours, the dose of NB-UVB irradiation is increased in 10%–20% increments until a single dose of 3.0 J/cm² is reached (skin phototype III or IV). If a persistent erythema reaction lasts for more than 72 hours or blistering occurs at the treated sites, the treatment schedule is delayed or the dose is reduced by 20%–50% of the last dose. If the erythema reaction resolves within 24–72 hours, the same dose is administered again. For targeted phototherapies using a 308 nm excimer laser and 308 nm MEL, the selections of the starting dose setting and subsequent dose changes are made in accordance with the recommendations for NB-UVB-based phototherapy.

Whole-body NB-UVB phototherapy

Whole-body NB-UVB phototherapy is suitable for NSV or mixed vitiligo, particularly for patients with widespread or extensive lesions. NB-UVB phototherapy is performed two to three times per week. The setting of the starting dose and the adjustments of subsequent doses are similar to those for localized phototherapy. The therapeutic effect of NB-UVB phototherapy in vitiligo does not always increase proportionately with the treatment number, frequency, MED, and cumulative dose. However, high cumulative doses of NB-UVB are more likely to cause adverse effects, such as xerosis, pruritus, and photoaging. The incidence of unresponsiveness to phototherapy (also termed the plateau phase) may be affected by the treatment number, frequency, MED, and cumulative dose.¹² The plateau phase refers to a period of time in which the patient fails to respond with significant repigmentation after consecutive NB-UVB exposures, usually more than 20 times. The following strategies are used to overcome the limitations of the plateau phase. (1) Phototherapy is discontinued for at least 3–6 months, allowing the skin to restore its photo-responsiveness. When a new session of phototherapy is restarted, the dose is usually started at the MED rather than 70% of the MED as used in the initial phototherapy. (2) If no repigmentation is clinically discerned after 3 months of treatment or the repigmentation rate is less than 25%, no further UVB treatment is needed. (3) Persistent repigmentation in vitiligo often requires phototherapy for a long duration. (4) A starting dose of 100 mJ/cm² of UVB is used for patients with rapidly progressive vitiligo, combined with systemic corticosteroids, thereby preventing a UVB-induced isomorphic reaction (Koebner phenomenon). In general, the repigmentation outcomes of patients who have had NSV for a short duration are better

than those of patients who have had SV for a long duration. The depigmented macules on the face and trunk respond more favorably to phototherapy than those on the extremities. Whole-body NB-UVB phototherapy is effective not only in arresting rapid disease progression, but also in inducing repigmentation.

Treatments used in combination with phototherapy

Phototherapy combined with other modalities achieves a superior efficacy compared with monotherapy. The co-treatments of choice are oral or TCS, TCI, oral Chinese herbal medicine and ready-made medicine, topical vitamin D3 analogs, topical psoralen-containing preparations, autologous transplantation, oral antioxidants, fractional laser therapy, dermabrasion, and fractional laser treatment combined with TCS.

Use of TCIs

TCI (tacrolimus ointment and pimecrolimus cream) are particularly efficacious in treating neck and facial vitiligo. For periorbital vitiligo, TCI may serve as the first-line treatment. TCI can also be applied on sensitive anatomic locations such as the genital region and labial mucosa.¹³ Topical application of calcineurin inhibitors is usually required for 3–6 months or longer when used in an intermittent manner. Unlike steroids, TCI do not cause serious adverse effects. However, TCI may induce or exacerbate skin infections, such as folliculitis, acne, and herpes simplex.

Use of vitamin D3 derivatives

Topical calcipotriene and tacalcitol ointment are applied twice daily to treat vitiligo.¹⁴ Vitamin D analogs are preferably used in combination with NB-UVB or 308 nm excimer laser treatments, or with TCS and TCI.¹⁵ Topical vitamin D analogs may enhance the efficacy of NB-UVB phototherapy.

TCM and Chinese herbs

The combination of TCM disease differentiation and syndrome differentiation can be divided into the progressive stage and the stable stage. The four main TCM syndrome types are wind-damp and heat stagnation syndrome, liver qi stagnation syndrome, liver and kidney deficiency syndrome, and the syndrome of blood stasis obstructing the collaterals. The progressive stage presents as wind-damp heat stagnation syndrome and liver qi stagnation syndrome, while the stable stage comprises liver and kidney deficiency syndrome and the syndrome of blood stasis obstructing the collaterals. Children with vitiligo often show weakness of the spleen and stomach. In the advanced stage of treatment, the main methods are to expel pathogenic factors, disperse wind, clear heat and drain dampness, disperse liver toxins and relieve depression. In the stable stage, the main treatment methods are to

nourish the liver and kidney, promote blood circulation, and remove blood stasis. In accordance with the lesion locations, the medicine corresponding to the appropriate meridian is selected.

Use of depigmentation agents

If more than 95% of the BSA is affected by depigmented macules and there is no repigmentation response to various routine treatments, depigmentation should be considered. A strict sunscreen regimen is required for depigmented skin to prevent sunburn or repigmentation of the treated residual normal skin upon sun exposure.

Topical depigmentary agents

Topical depigmentary agents include 20% monobenzone (monobenzyl ether of hydroquinone) applied twice daily for 3–6 months and 20% 4-methoxyphenol (mequinol, monomethyl ether of hydroquinone) applied twice daily. The initial concentration of mequinol is 10%, with the concentration increased every 1–2 months until satisfactory depigmentation is achieved. The residual pigmented macules in exposed locations are treated first, followed by those in unexposed locations. Depigmentation treatment is usually required for 3–6 months. Systemic absorption of depigmentary agents should be minimized, and the patient should ensure that they have no skin contact with others for 2–3 hours after topical application.

Laser therapy

The Q-switched lasers (Q755 nm, Q694 nm, and Q532 nm) selectively destroy melanocytes and can be used for depigmentation treatment.

Use of camouflage

Camouflage is an important therapeutic modality for patients with depigmented macules on exposed sites. Camouflage cosmetic creams often contain dihydroxyacetone (a brown dye for skin staining), which makes the vitiliginous skin blend in completely with the normal surrounding skin.

Surgical treatments

Surgical treatment is recommended primarily for patients with stable vitiligo (no new lesions or expansion of lesions for more than 1 year), specifically those with unclassified SV. Surgery is also considered for patients with limited lesions of other vitiligo types on exposed skin sites. The following factors must be considered before the surgical procedure is performed. Clinical assessment of the location and area of vitiligo lesions is needed before selecting autologous transplantation. Surgical procedures are not applicable to patients with active vitiligo and keloids. The frequently used surgical procedures include suction blister autologous epidermal grafting, minigrafting, ultrathin epidermal grafts, transplantation of autologous non-cultured epidermal cell suspension or autologous cultured

melanocytes, single hair follicle transplantation, and transplantation of tissue-engineered epidermal substitutes. Autologous epidermal grafting is an effective and relatively simple surgical procedure. UVB phototherapy is often administered after the transplantation, and greatly improves the repigmentation outcome.

Childhood vitiligo

Moderate-potency TCS are administered to treat vitiligo in young children (<2 years old); intermittent topical administration is preferred to ensure safety. High- or moderate-potency TCS are prescribed for children older than 2 years. Tacrolimus ointment and pimecrolimus cream are particularly recommended for childhood vitiligo.^{13,16} Published studies and clinical experience regarding the treatment of infant atopic dermatitis with TCI suggest that TCI should also be considered for infant vitiligo.¹⁷ Topical vitamin D analogs can be used for childhood vitiligo.^{16,18} For children with rapidly progressive vitiligo, a low dose of oral prednisone (5–10 mg per day) is recommended for 2–3 weeks, and oral prednisone can be given again after an interval of 4–6 weeks if needed. Localized phototherapy is another treatment option for childhood vitiligo.

Auxiliary therapies

Health education should be emphasized for all patients with vitiligo. It is beneficial to avoid unhealthy psychological stress, avoid undersleeping and fatigue, and prevent exposure to phenolic compounds. Daily intakes of vitamin C-enriched fruits and vegetables and a balanced diet and nutrition are highly recommended. The implementation of dietary restrictions may be an inappropriate approach for vitiligo, especially in its progressive stage. Supplements of vitamin B, vitamin E, folic acid, calcium, selenium, and antioxidants are considered beneficial.

Maintenance therapy

Maintenance treatment is required for an additional 3–6 months after the achievement of complete or satisfactory repigmentation. TCI are used once or twice weekly for 3–6 months to prevent disease relapse and re-depigmentation.¹⁹ TCM and Chinese herbs are also used as maintenance treatment based on the TCM disease differentiation and syndrome differentiation. Once maximum repigmentation has been achieved, maintenance phototherapy treatment should be continued twice a week for the first month, once a week for the second month, and once every 2 weeks for subsequent months.²⁰

Prospects

Based on deep insights into the immunological mechanism underlying vitiligo, multiple small-scale clinical trials show that topical or systemic applications of JAK inhibitors are promising treatments for vitiligo.²¹

Additional remarks

There is no guarantee that the treatments recommended by this consensus will achieve satisfactory repigmentation outcomes in all patients.

This consensus does not cover all current medications or modalities used to treat vitiligo.

Early intervention and personalized or combined therapeutic modalities are critical to achieve greater responses, including western medicine combined with TCM and Chinese herbs, topical combined with systemic administration, and medication combined with physical therapies or surgical treatments. The treatments should be long-term, with every therapeutic course lasting for at least 3 months.

Several topical medications (such as tacrolimus, pimecrolimus, calcipotriol, and tacalcitol) are still considered off-label for use in vitiligo, but have been proven to be effective for vitiligo treatment in clinical practice and in recently published studies. Informed consent is required before the prescription of these off-label medications.

The treatment regimens recommended for progressive vitiligo in children in this consensus are based on the keynote speech given by Prof. Pear E. Grimes at the 63rd annual meeting of the American Academy of Dermatology (2005) and the opinions of Chinese experts.

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