Guidelines of Vitiligo Management

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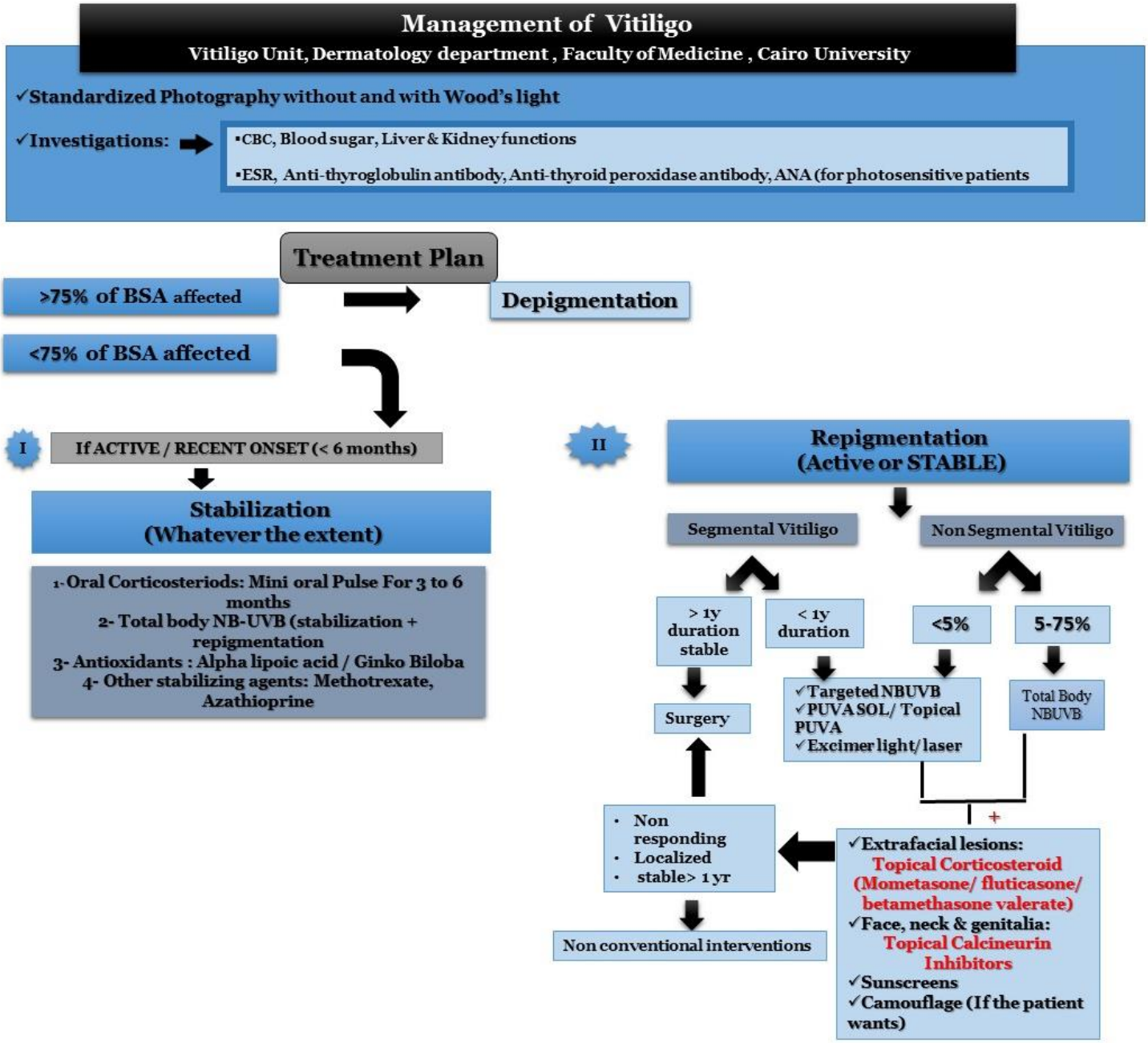

Vitiligo Management Algorithm, Vitiligo Unit, Dermatology Department, Faculty of Medicine, Cairo University. Complete blood count (CBC), Liver function test (LFTs), Kidney function tests (KFTs), Erythrocyte sedimentation rate (ESR), Anti- nuclear antibodies (ANA)

1. Introduction, stabilization and repigmentation as a target of treatment

Vitiligo is a skin disorder that results in the formation of depigmented patches. Despite being asymptomatic, it is cosmetically disfiguring[1, 2]. Based on the clinical morphology, vitiligo can be classified as segmental or non-segmental[3]. It can also be classified into progressive or stable depending on the activity of the disease. The treatment of vitiligo usually comprises two strategies. The first aims at providing disease stability by arresting the progression of active disease. The second strategy targets repigmentation of the depigmented lesions[4]. Accordingly, treatment of vitiligo should take these points into consideration and should be individualized according to each patient[5]. The duration of the disease is very important as early cases within the first few months have a much greater hope for response and longer control of the disease. Management in the early few months of the disease carries better prognosis as regards response rate and duration of remission. Both stabilization and repigmentation must be aimed at as early as possible [6].

2. Diagnosis and evaluation

<u>On first visit</u>

All patients with suspected or confirmed vitiligo, whether the diagnosis is suspected or confirmed, seeking medical advice in the Outpatient Dermatology clinic, Kasr Al Ainy hospital are referred to the Vitiligo unit.

Usually the diagnosis is clinical, however every patient is subjected to a stepwise diagnostic scheme.

1. History taking:
    a. Thorough history-taking.

    Special attention should be given to the onset (early onset is associated with a better prognosis), course (progression or possible repigmentation), Koebner's phenomenon (different forms of trauma including rubbing of the skin during application of topicals), occupation (especially exposure to any chemicals), family history and presence of co-morbidities (vide infra).

    b. Activity is assessed via the VIDA[7] and VSAS[8] scores**.**

2. Examination
    a. Full dermatological examination, including the genital areas and scalp (hair graying), is done to confirm the diagnosis and exclude any associated skin diseases.
    b. Examination of the vitiliginous lesions with focus on presence of white hairs, inflammation, mucosal affection, koebnerized lesions.
    c. Examination under Wood's light is to determine disease extent
    d. VES plus score[9] is done.
    e. Dermoscopy can help for detection of the color of fine hairs and dermoscopic signs of activity[10]
    f. Photography of the whole body guided by standardized serial photography for assessing and monitoring vitiligo[11] without and with Wood's light **(Figure 1)**.
3. Investigations
    a. Punch biopsy is taken from at least 2 lesions in questionable cases.
    b. Laboratory tests including; Complete blood count (CBC), Liver function test (LFTs), Kidney function tests (KFTs), Erythrocyte sedimentation rate (ESR), Anti- nuclear antibodies (ANA), Thyroid profile, Anti-throglobulin and anti-thyroid peroxidase antibodies.
4. Patient education

Discussion with the patient or guardian for those below 18 during the first visit is very important to reach a doctor/patient agreement about the aim and expected results of therapy. Patients then are instructed that strict compliance to treatment and attendance of follow- up visits is mandatory. Reassurance is important as regards to the non-infectious nature of vitiligo and the satisfactory results of therapy regimen customized for each patient, especially with early management.

3. On follow-up visits

Patients are required to attend monthly follow-up visits, to monitor therapeutic efficacy. Wood's light, VES plus and VIDA, VSAS scores and photography are done.

4. Systemic stabilization

4A Narrow band UVB as a stabilizing tool

NB-UVB is a management pillar in treatment of vitiligo. Not just does it act as the main tool for repigmentation of vitiligo[12], it plays an important role in vitiligo stabilization [12, 13, 14] through its systemic immunomodulatory effect [12, 15]. The importance of this is highlighted whenever systemic corticosteroids; the cornerstone of vitiligo stabilization[16] are contraindicated or immunosuppression is not justified. This is of due importance in pregnant and lactating females, uncontrolled diabetic and/ or hypertensive patients as well as immune-compromised individuals.

4B. Oral Mini-pulse (OMP)

Oral mini pulse (OMP) is the use of a higher than the usual daily doses of oral steroids in an intermittent manner (2 consecutive days a week) to achieve good results while reducing possible side effects.

Indications: - It is used mainly to arrest activity in patients with rapidly spreading disease [17]. It has not been found to be very effective in re-pigmentation of stable vitiligo [18].

- Stable/Slowly progressive vitiligo with extensive involvement and frequent exacerbations.

- Patients with evidence of autoimmune disease (e.g. high anti-thyroid antibodies titers).

- With any surgical procedure to decrease the possibility of koebner phenomenon.

Mechanism of action: Oral corticosteroids have a broad immunosuppressive effect. They help modulate cell mediated immunity, induce T cell apoptosis in circulation and suppress autoantibody formation[19, 20, 21].

Dosage & treatment duration: Dexamethasone 2.5mg -5mg or Betamethasone 5-7.5mg on 2 consecutive days/week are given for 3-6 months' duration according to response. Studies have shown arrest of activity between 88%-91% of patients[22, 23]. OMP can be given alone or in combination with phototherapy for better results[18]. Treatment should be step-wise and gradually tapered.

Monitoring: Regular monitoring of blood pressure, blood sugar and weight should be done to assess risk-benefit and evaluate efficacy.

Side effects: The OMP regimen has significantly less side effects compared to typical daily dosing of corticosteroids[24]. Calcium supplementation, salt restriction and use of antacids can minimize risk of side effects. Weight gain, insomnia, acne, agitation, menstrual disturbance, and hypertrichosis are possible side effects[22].

Contraindications: There are very few absolute contraindications to use of systemic corticosteroids, such as systemic fungal infections and herpes simplex keratitis. Relative contraindications include congestive heart failure, human immunodeficiency virus (HIV), psychosis, active peptic ulcer disease, active tuberculosis, and septicemia. Well-controlled diabetes and hypertension are not contraindications; however, patient should be closely monitored and dose kept to the minimum[17].

4C. Steroid sparing agents

Methotrexate (MTX):

Indications: MTX in a weekly low dose (≤ 25mg/wk) can be used in patients with active vitiligo[25, 26]**,** whenever systemic corticosteroids are contraindicated as in uncontrolled diabetes mellitus, uncontrolled hypertension, osteoporosis, glaucoma and herpes simplex keratitis.

It could be used safely in combination with OMP as a steroid sparing agent to avoid relapses following steroid tapering and withdrawal, However GIT upset was more common than when used as monotherapy.[26]

Mechanism of action: MTX is a folic acid antagonist and an inhibitor of cell proliferation. MTX selectively induces apoptosis in activated, proliferating CD4 T cells. It also downregulates B cells.[27] MTX prevents leukocyte chemotaxis and inhibits monocyte and macrophage secretion of multiple cytokines, e.g. tumor necrosis factor (TNF)-α, IL-6, IL-10 and IL-12.[25]

Contraindications: contraindications include hypersensitivity to MTX, pregnancy, lactation, chronic liver diseases, immunodeficiency syndrome, bone marrow hypoplasia, leukopenia, thrombocytopenia and significant anemia as well as active infection.[28]

Monitoring: baseline investigations include complete blood cell and platelet count, liver function tests (including HBV and HCV screening), renal function tests, pregnancy test and chest X-ray (to exclude latent TB).[29] Due to the risk of myelosuppression and hepatotoxicity, laboratory monitoring is recommended within one week of start dose and every 2 weeks during the first 1-2 months, then every 2-3 months**.**[30] Due to risk of teratogenicity women during childbearing bearing

period as well as men receiving MTX should undergo adequate contraception during treatment as well as 3 months after stoppage of treatment in men and for one ovulatory cycle in women.[31] Non-steroidal anti-inflammatory drugs (NSAID), trimethoprim-sulphamethoxazole, ciprofloxacin, phenytoin and thiazide diuretics may increase MTX toxicity.[32]

Dosages & duration of treatment: 0.2-0.4 mg/kg (maximum dose 25mg/wk) once weekly either orally, intramuscular or subcutaneous. Oral administration could be divided into 3 doses 12 hrs apart which may reduce drug toxicity.[33] Oral folic acid supplementation in a dose of 2.5mg daily is recommended daily except on MTX day. Currently there are no sufficient studies on the ideal duration of treatment.

Azathioprine (AZT)

Indications: AZT is considered a good alternative whenever OMP is contraindicated and as a steroid sparing agent to avoid relapses during steroid tapering. We recommend using it in combination with OMP from the start and not to delay its initiation during OMP tapering as a previous studies found that stabilization is achieved 4-6 months after starting AZT in active vitiligo with comparable results to corticosteroids and less side effects.[34-36] However further studies are needed to evaluate the safety of combining ATZ with phototherapy and the potential risk of non melanoma skin cancer (NMSC).

Mechanism of action: inhibits T and B lymphocytes.[34]

Contraindications: impaired liver functions, impaired bone marrow function, severe active infection, known malignancy, pregnancy and lactation. Dose of AZT should be reduced in patients with renal impairment, however those on dialysis could receive full dose.[37]

Monitoring:

Patients should do the following baseline blood tests, CBC, liver function tests, kidney function tests, electrolytes, HBV and HCV serlolgy (HBsAg and HCV antibodies). Annual TB screening and Thiopurine methyl tranferase level (TPMT). Blood tests should be repeated every 2 weeks during the first 3 months and then every 2 months.[38]

4D.Systemic antioxidants

Different systemic anti-oxidants can help in treatment of vitiligo including gomgko biloba, alpha lipoic acid and polypodium leucotomous[39-43].

Gingko biloba:

Gingko biloba is one of the oldest trees on earth, its leaves and seeds have been used in medicine for a long time.[39] Gingko biloba was found to be effective in arresting activity of slowly progressing vitiligo after 6 months of a daily oral dosage of 40 mg tds[40] **or** 60 mg bid**.**[41]

Mechanism of action: Its exact mechanism of action in vitiligo is not fully understood but could be attributed to the antioxidant, anti-inflammtory and immunmodulatory properties of the drug.[40]

Indications: We recommend as an adjuvant treatment in combination with phototherapy.

Dosages: It is available as oral capsules and tablets in different concentrations and also as oral drops (40mg/ml). The recommended daily dose is 40 mg to 60mg, 3 to 4 times a day (average daily dose 120mg/day).[39]

Contraindications: There are no known contraindications; however Ginkobiloba should be used with caution in patients receiving anticoagulant/antiplatelet therapy or having bleeding disorders due to its anti-platelet properties. Ginkobiloba is not recommended during pregnancy, lactation and in children,[39] however it was used safely in children (> 6 yrs) with ADHD in a gradually increasing oral daily dosage of 80mg/day in those with a body weight < 30 kg and 120 mg/day for those > 30 kg.[42] **Side effects:** Gastrointestinal side effects and restlessness have been reported with doses > 240mg/day.[43]

5. Phototherapy and excimer laser

Phototherapy

I. <u>Narrow-Band Ultraviolet Light B (NB-UVB)(311 nm):</u>

When it comes to repigmentation of vitiligo, NB-UVB stands as the sole main tool in this regards[12], hence it is used constantly in combination with all other therapeutic measures.

Phototherapy recommendations modified from The Vitiligo Working Group phototherapy recommendations [44]

A. Frequency of administration

Optimal: 3 times per week

Acceptable: 2 times per week

B. Fixed dosing based on SPT

Initiate dose at 500 mJ/cm^2 for skin phototypes (SPT) III-V, 300 mJ/cm^2 for SPT I, II

C. Maximum acceptable dose

Face: 2500 mJ/cm^2

Body: 5000 mJ/cm^2

D. Non photoadapters:

Use non-steroidal anti-inflammatory drugs (ibuprofen 400 mg) before session[45]

E. Maximum number of exposures: No consensus for maximum number of sessions, however, high safety profile was reported for up to 500 sessions especially in darker skin phototypes [46].

F. Course of NBUVB:

a. First Assessment treatment response after 18-36 exposures
b. Minimum number of sessions needed to determine lack of response usually 48 exposures

G. Dose adjustment based on degree of erythema

No erythema: increase next dose by 10-20% in subsequent sessions.

Pink asymptomatic erythema: hold at current dose until erythema disappears then increase by 10-20%

Bright red asymptomatic erythema: stop phototherapy until affected areas become light pink, then resume at last tolerated dose

Symptomatic erythema (includes pain and blistering): stop phototherapy until the skin heals and erythema fades to a light pink, then resume at last dose showing pink erythema.

H. Dose adjustment following missed doses

4-7 days between treatments: hold dose constant
8-14 days between treatments: decrease dose by 25%

15-21 days between treatments: decrease dose by 50%

Over 3 weeks between treatments: restart at initial dose

I. Device bulb replacement

Must be followed by 10-20% decrease in dose

J. Outcome measures to evaluate response

Serial photography to establish baseline severity, disease stability, and response to treatment

Validated scoring systems, such as the VASI or VES plus, to quantify degree of response.

K. Posttreatment recommendations

Application of sunscreen

Avoidance of sunlight

L. Topical products before phototherapy

Avoid all topical products for 4 hours EXCEPT mineral oil

Mineral oil can be used to enhance light penetration in areas of dry, thickened skin, such as the elbows and knees

M. Tapering NBUVB after complete repigmentation has been achieved

First month: phototherapy twice weekly

Second month: phototherapy once weekly

Third and fourth months: phototherapy every other week

After 4 months: discontinue phototherapy

N. Follow Up

SPTs I-III: yearly follow-up for total body skin examination to monitor for long term adverse effects of phototherapy

SPTs IV-VI: no need to return for safety monitoring as no reports of malignancy exist with this group

All patients: return upon relapse for treatment

O. Minimum age for NBUVB in children

Minimum age is when children are able to reliably stand in the booth with either their eyes closed or wearing goggles

Typically around 7-10 years of age

P. Treatment of eyelid lesions

Keep eyes closed during treatment, using adhesive tape if necessary

Q. Special sites

Cover face during phototherapy if uninvolved

Shield male genitalia

Protect female areola with sunscreen prior to treatment, especially in SPTs I-III

R. Combination treatment for stabilization

Oral antioxidants

Topical treatments

OMP corticosteroids

S. Treatment of NBUVB induced skin changes

Xerosis: emollient or mineral oil

Skin thickening: topical corticosteroids or keratolytics.

II. Photo-chemotherapy Ultraviolet A (PUVA):

- Systemic PUVA:
    - Oral PUVA is now considered second line therapy due to lower efficacy compared to NB-UVB and more long as well as short term side effects[47].
- Topical PUVA/ PUVA sol (recommended for localized disease):
    - Different topical photosensitizers including 8 methoxy psoralen (MOP) at very low concentrations starting at 0.001%, Khelin 2% or oil of bergamot starting at 25% concentration can be applied 30 minutes before exposure to solar light (if machines are not available) (PUVA sol)[47, 48] or UVA (Topical PUVA)[47- 49,].
    - Topical PUVA has the advantage of being safe, with lower cumulative dose and negligible systemic side effects compared to oral PUVA[47, 50]. Nevertheless, it lacks systemic stabilizing effect on active vitiligo as well as causing perilesional hyperpigmentation and blistering reactions[47].
    - Initial dose: Sessions are started at 0.5 J [51].
    - Follow the same guidelines as NB-UVB, apart from maximum dose of up to 10 J being less erythemogenic.

Regarding PUVA sol, patients are taught about gradual increase in the duration of UV exposure and to tailor their exposure to development of faint erythema lasting ≤48 hours.

III. Excimer Light/ Laser (recommended for localized disease):

- Monochromatic 308 nm high fluence light or laser targeted devices have been developed, offering the advantage of more rapid response with fewer sessions [52, 53]. However; being targeted, they lack stabilizing effect on active vitiligo and are suitable only for localized vitiligo[47].

It is noteworthy targeted light therapies lack the ability of stabilization of the total body NBUVB, therefore they cannot be considered as monotherapy in active disease[47].

Patient Monitoring:

Base line: Complete sheet and evaluation of extent (VASI, VES) and activity (VIDA)
Weekly: clinical assessment
Monthly: Clinical, photographing VSAS & VIDA,
Every 3 months: photograpy and evaluation of extent (VASI, VES) and activity (VIDA & VES)
Evaluation at Session 48 discharge if no response at all.
Evaluation at session 70: If repigementation reaches 25% or less phototherapy is discontinued.
Phototherapy is to be continued as long as there is ongoing improvement.

6. Topical treatment

Topical corticosteroids (TCS)

We recommend their use on limited areas and on recent lesions.[54] TCS could enhance repigmentation over elbows and knees, however poor results were noticed over distal exterimities.[55] A twice daily application of a mid-potency or a single daily application of a high potency topical corticosteroid could be used.[56] Local side effects remain a concern with topical corticosteroid usage therefore we recommend topical preparations with a lower risk of local side effects such as class III TCS mometasone furoate [47] and fluticasone propionate[57].Topical calcineurin inhibitors (TCIs) are preferred in areas at a higher risk of local side effects such as face, flexures and genital areas. There are no sufficient studies on the ideal duration of usage, however we recommend continuous usage for no longer than 3 months, Some authors allow topical corticosteroids use for six months provided that they interrupt usage for one month after the initial 3 months. Others recommend a discontinuous regimen (15 days per month for 6 months) [47].

Topical Calcineurin inhibitors (TCIs)

Many studies have demonstrated the efficacy of both tacrolimus and pimecrolimus as monotherapy and in combination with phototherapy, once and twice daily applications were found effective[58]**,** however we recommend a twice daily application**.** Two preparations are available for tacrolimus 0.03% and 0.1%. TCIs provide a good alternative to TCS in areas at a high risk for skin atrophy such as the face, flexures and genital areas particularly in children. UV exposure has been found to enhance their therapeutic effect[59], therefore best results are noticeable in the head and neck region[60] and in combination with Nb-UVB.[61] Their efficacy in anatomical sites other than the head and neck has not been confirmed in absence of occlusion.[62] Genital areas were found to

respond poorly[63] We agree with previous recommendation of a continuous usage for at least 6 months if found effective, prolonged treatment (> 12 months) could be considered**.**[47] The most commonly reported side effects include application site transient burning sensation, pruritus and erythema[58].

7. Surgical treatment

Indications: The option of surgery is classically for patients with segmental vitiligo. However, patients with stable localized vitiligo, resistant to other medical interventions are also candidates for surgery[64]. In NSV a period of stability ranging from 6 months to 2 years, and absence of a Koebner isomorphic response are recommended[65].

Mechanism of action: Surgical treatments are based on the principle of transplanting autologous melanocytes to affected areas, either by tissue or cellular grafting techniques[66]. In NSV surgery is better combined with other medical and or UV-light treatment for best outcome and long-term stability[47].

Types of surgery: Vitiligo surgery could be classified according to the type of the graft into tissue grafts and cellular graft[67].

The common, easy and inexpensive method of tissue grafting is **mini punch grafting** (tissue graft), but it is not suitable for large lesions and seldom produces even repigmentation.

Cellular grafts, consist of a basal cell layer autologous suspension containing epidermal cells (melanocytes and keratinocytes) that are first harvested from autologous donor skin and then transplanted (with or without prior selective cultivation) onto vitiliginous recipient sites[68]. Unlike tissue grafts, cellular grafts can be used to treat large areas using a small amount of donor tissue.

Cellular grafting can be broadly categorized into; cultured and non-cultured cellular grafting. In the last years, **non-cultured epidermal cell suspension transplantation (NCES)** is considered the standard vitiligo surgery[69]. NCES can be performed in 1 day with a donor-recipient ratio up to 1:10[70].

Side effects: Mini punch grafting may cause pigment and textural variations such as cobble-stoning and holds a risk of scarring and keloids[65]. Rare side-effects (temporary depigmentation at donor site and transient post inflammatory hyperpigmentation at recipient site) have been observed with cellular grafting[71].

Contraindications: Recent disease activity and presence of koebner phenomenon.

8. Depigmentation

Depigmentation of the normal skin is indicated in vitiligo universalis. Patients with widespread vitiligo, refractory to all forms of repigmentation can also benefit from depigmentation of normal skin in the face and hands to attain cosmetically better appearance.[72] Different methods of depigmentation are available including:

1) Monobenzyl Ether of Hydroquinone (MBEH):

   MBEH is the mainstay of vitiligo depigmentation.[73] Different concentrations of MBEH can be utilized, but MBEH 20 % is the most used due to its tolerability and satisfactory outcome. It should be applied twice daily, till complete depigmentation is achieved. Sunscreens, preferably physical sunscreens as zinc oxide 10% should be regularly applied throughout the treatment period and thereafter. Adverse effects include skin irritation which manifests by burning sensation, erythema, dryness, or edema, and should be treated by temporarily stopping treatment, application of cold compresses and emollients, then resuming treatment gradually at every other day or once daily dose. Initial skin darkening can occur at the first month of treatment. Distant depigmentation occurs in some patients, but ochronosis is rare side effect that occurs after prolonged use of MBEH.[72-74]

2) Q- switched laser (1,064/532 nm):

   Q-switched laser is effective for depigmentation of residual areas of facial normal skin. The simultaneous use of the 1,064 nm and 532 nm wavelengths enhances the depigmentation effect of the Q-switched laser.[75] The 532 nm targets the epidermal pigment,[76] whereas the 1,064 nm can penetrate deeply affecting both basal and follicular melanocytes which might reduce the incidence of repigmentation. One pass of 1.064 nm Qs Nd:YAG laser (Fotona, EU)is performed [spot size: 4 mm, power: 8 J/cm2] followed by frequency doubled KTP laser (532 nm) [spot size: 3 mm, power: 1.5–2 J/cm2] in the same session. Multiple sessions are usually needed to achieve complete depigmentation. Adverse effects include mild pain during the session, erythema, petechiae and crustations.[75]

3) Other depigmenting agents:

   TCA 25% and 50% can be used for large facial areas, as they are easy, safe, and affordable. For extrafacial skin, cryotherapy, and phenol 88% are useful with special consideration to the limitations of each modality. TCA peel 25% is applied in 2 to 3 coats, with 2-minute

interval, after skin degreasing, while TCA peel 50% is applied in one coat. Side effects of TCA peels are burning pain and erythema. Phenol peel 88% is applied in one pass to a localized spot (<20% of affected area) and patients should be instructed to drink ample fluids before and during sessions to enhance phenol metabolism and excretion. Cryotherapy is performed using cotton-tipped swabs to lightly brush liquid nitrogen (−196 °C) in 2 freeze cycles lasting 5–10 seconds with 5 seconds thaw interval. Side effects of phenol peel and cryotherapy include pain, erythema and crustations.[75]

9.Non-Conventional treatments

A number of non-conventional options in vitiligo treatment have been investigated in the past 2 decades that may increase chances of treatment success in terms of repigmentation of resistant lesions. Being essentially based on effect of trauma, one year stability is a prerequisite prior to attempting any of these modalities[77-92]. These options include:

1. Needling/ Micro-needling
    - For needling, insulin syringe is placed almost parallel to skin surface, 2-3 mm from the edge into the vitiliginous patch, doing 4-5 insertions/ cm either from surrounding normal skin or pigmented island within the lesion[78].
    - For micro-needling, 0.25-2 mm depth is used based on skin thickness with pinpoint bleeding set as the endpoint, moving in all directions across the lesion, starting 2-3 mm from edge[79-81].
    - It is proposed that it helps repigmentation via mechanical transfer melanocytes from pigmented to non-pigmented areas[77-81] and by trauma induced inflammation and influx of cytokines[78]. Furthermore, it creates micro-pores that allows for trans-epidermal delivery, thus increasing efficacy of any applied topical treatment and decreasing the required treatment duration[79, 80].
2. Platelet rich plasma (PRP)
    - Ten millimeter venous blood centrifuged by double spin technique (soft spin: 1500 rotation per minute (rpm) for 15 minutes followed by hard spin for the supernatant: 3000 rpm for 10 minutes) [82].
    - PRP works by both immune-modulatory and growth promoting effect via multitude of growth factors together with the effect of needling[83].

3. Laser Dermabrasion
    - Laser dermabrasion using fractional lasers. Fractional carbon dioxide (CO2) laser is more readily available. We recommend the following parameters based on previous work by El-Mofty et al., 2016 (power 10 watt, spacing 500, dwell 1000, stack 1)[81].
    - The proposed theories include inducing inflammatory cytokines that overrule melano-cytotoxic T cells. Additionally, laser assisted drug delivery of different topical treatments as well as enhancing penetration of phototherapy and reducing required cumulative dose[84-90].

4. Chemical Peels
    - Trichloroacetic acid (TCA) is the most commonly used chemical peel. We recommend lower concentrations (15-25%) [81].
    - Chemical peels are hypothesized to work through reverse koebnerization and inducing post inflammatory hyperpigmentation with more favorable outcomes in skin of color where it increases melanogenesis and melanin transfer to keratinocytes[81, 91]. Additionally, TCA 25% have been reported to facilitate dermabrasion in vitiligo surgery[92].
5. Combination with topical treatment
    - Different topical treatment can be combined to different non-conventional modalities to optimize treatment response and enhance drug delivery. For instance, topical clobetasol/ betamethasone dipropionate/ tacrolimus, PRP or 5- fluoro-uracil can be added on laser dermabraded vitiliginous resistant patch or following micro-needlng[79, 80, 84-87, 89, 90].

10.Camouflage

Camouflage can be used as an adjuvant modality to vitiligo treatment to conceal vitiligo lesions and increase the patients' confidence, self-esteem, and compliance to therapy.[93] Camouflage may be permanent or temporary.[94] Permanent camouflage is obtained by a cosmetic tattoo, which is formed of inert iron oxides available in more than 15 shades.[95] The color is implanted in the

dermis with specialized techniques. Satisfactory results are obtained only in small areas, particularly in the lips. Dark photo types are more easily treated than people with fair skin.[96]

Temporary cosmetic camouflage can be obtained by applying uniform thin films of selected opaque cosmetics containing light-reflecting ingredients. Products for covering vitiligo are specific and quite different from other common cosmetic make-ups.[94] The basic approaches to camouflage cosmetics are contour correction, color correction, or a combination of both. Pigmentation defects can be camouflaged by applying an opaque cosmetic that allows none of the abnormal underlying skin tones to be appreciated. The vitiliginous lesions should be covered by foundations with the appropriate amount of brown pigment to hide the defect. Finally, facial powders that match the skin tone may be applied to set the camouflage makeup and prevent it from smudging off.[94]

Technique of application[94]

1. Cleanse the skin.
2. Assess skin tone to choose the make-up base shade which is close to the patient's natural skin color.
3. Blend with other shades of color to match the patient's skin tone. No more than three colors should be combined. Blending is performed by applying small amount of the make-up to the back of the hand.
4. Apply cream in a thin coat from the center of the lesion and blend into the normal skin. For extensive lesions, camouflage can be applied to lesional borders where contrast was most pronounced to merge vitiligo with the surrounding skin and make the contrast less noticeable. Wait for 5 min for setting of cream.
5. Press the fixing powder on top of the foundation with cotton wool. After 10 minutes, eliminate any excess powder with a brush.
6. It takes one hour for color to settle and become waterproof, nongreasy, and resistant to sunlight and smudging so that it will not rub off on clothing.

Self-tanning products contain dihydroxyacetone 3–5% (DHA) are easy to apply as they are neither dirty nor greasy. DHA is a sugar that binds with the amino acids of the stratum corneum, to induce the production of colored components that change yellow to brown, giving the skin a tanned effect.[93-94]

11. Combination therapy:

Treatment of vitiligo requires combination of different modalities involving phototherapy as a management pillar[12]. Combination Therapy Measures in addition to Phototherapy includes:

a) Antioxidants[39-43].

b) In extrafacial lesions, once-daily thin application of potent TCs such as; for a period no longer than 3 months with daily application, or 6 months for alternate day application with a strict assessment of response based on photographs[54-57].

c) Facial, neck & genital lesions are treated by topical calcineurin inhibitors (TCIs) 0.1%, 2/day/6 months. During this period, moderate daily sun exposure is allowed. If effective, prolonged treatment (e.g. longer than 12 months) may be proposed[58-63].

d) Stabilizing therapies other than phototherapy involving MOP and other steroid sparing agents for active disease[17-38].

e) Camouflaging: is to be advised in patients with visible vitiligo[93-96].

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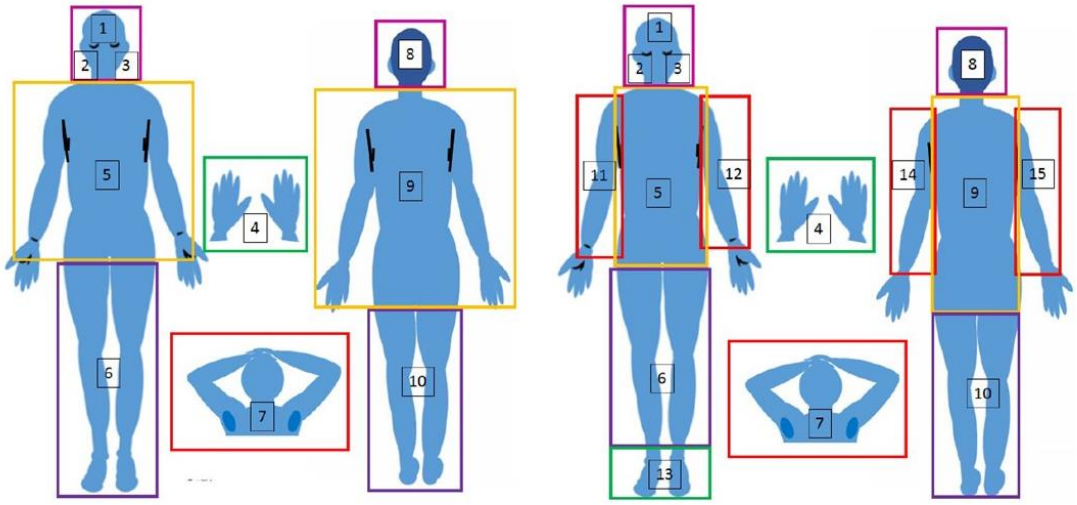

Figure 1: Standardizing serial photography for assessing and monitoring vitiligo (van geel et al., 2020)