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REVIEW ARTICLE

An Updated Overview about Management of Vitiligo: A Review Article

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ABSTRACT

Background: The achromic macules and patches seen in vitiligo, which is a multifactorial condition, are caused by a decrease in skin pigmentation. In order to halt the advancement and stimulate skin repigmentation, there are presently a number of medicinal treatments that can be used. The pigmentation effects of these treatments, whether used alone or in combination, have been varied, but generally speaking, they have been safe and successful. There is currently no cure for vitiligo, and no treatment has been shown to reliably restore pigmentation in most patients. Depending on geographic location, clinical presentation, and the existence of disease activity, personalized treatment plans are most effective. We intended to provide an outline of different updated lines of treatment for vitiligo because it is a tough condition and because management regimens may differ for patients of different races and skin colors.**Conclusions:** A number of variables influence the therapeutic approach selection process, including vitiligo distribution, type, patient age, as well as skin phototype. Researchers have found that vitiligo sufferers are more likely to suffer from depression, and the condition itself can have a major impact on their daily lives. Immunosuppressants, including topical and oral, phototherapy, and surgical procedures are common methods of management. Conventional medicine, on the other hand, has a poor response rate, frequent side effects, and a high recurrence rate.

Keywords: Updated, Vitiligo, Management

INTRODUCTION

Vitiligo is a disorder characterised by hypopigmented or depigmented patches which may be caused by the death of skin melanocytes, Melanocyte death can occur in a number of places, including the skin and mucous membranes. Possible causes include inherited traits, friction and other environmental factors, changes in metabolism, and abnormalities in inflammatory and immunological responses [1].

Its incidence is 1% worldwide and does not vary much by gender, race/ethnicity, or area, although girls and women are more likely to seek advice than boys and men, maybe because of the more severe societal consequences. Two clinical forms of vitiligo, known as segmental and non-segmental (localised or generalised), differ in the symptoms and signs they manifest [2].

Depigmented areas having a recognised cause, such as those that appear after a burn, exposure with chemicals like phenol, or an inflammatory skin illness, are called leucoderma. In contrast to vitiligo, it does not worsen if the underlying cause is eliminated [3].In most cases, vitiligo can be diagnosed simply by looking for the following symptoms: a uniform distribution of acquired, nonscaly, amelanotic, chalky-white macules with clear borders: zones of friction, periorificial, lips, distal extremity tips, penis, and segmental [4].

In light-skinned people in particular, the magnified lesions visible under Wood's lamp examination make vitiligo more apparent. Dermoscopy and Wood's light help doctors distinguish between chronic and acute skin conditions. Objective activity signals such as confetti-like lesions, hypochromic borders and koebnerization which are inconspicuous

in room light in individuals with lighter skin phototypes—are emphasised by wood's light. Nevertheless, doctors should learn how vitiligo lesions' autofluorescence differs from that of other hypopigmented disorders and skin dyschromia [5].

Confirmatory laboratory tests are typically unnecessary for diagnosing vitiligo. Other than ruling out other possible illnesses, no procedures, including a skin biopsy, are required. In vivo confocal microscopy and skin biopsies are non-invasive ways to determine if a lesion contains melanocytes. There are no melanocytes, and the epidermis has lost all melanin pigment, according to the histology of a vitiligo lesion's central region. At the periphery of the lesions, you could see lymphocytes every once in a while, [6].Vitiligo can be distinguished from other depigmenting conditions with the help of dermoscopy. In contrast to other hypopigmentation illnesses, vitiligo is characterised by the presence of telangiectasia and persisting perifollicular pigmentation. Moreover, it can be helpful in determining the progression of vitiligo and the degree of disease activity: Perifollicular pigmentation is observed in progressing lesions, while perifollicular depigmentation is observed in stable or remitting lesions [7].

Treatment of vitiligo

Treatment for vitiligo is difficult, and patients of different races and ethnicities may require unique approaches. Several aspects determine the therapy technique to be used, including as the type of vitiligo, the distribution of skin lesions, the patient's age, and skin phototype. Vitiligo can severely diminish a person's quality of life, and research shows that depressive symptoms are common among vitiligo patients [8].Immunosuppresants, including topical and oral, phototherapy, and surgical procedures are common methods of management. However, traditional treatments typically take a long time to work, and patients generally experience unpleasant side effects and a high relapse rate. Treatments for vitiligo have included a wide variety of unapproved drugs [5].

I. Medical therapies:

A) Topical

1. Corticosteroids:

As a first line of defence against localised vitiligo, topical corticosteroids, especially those with a medium to high potency, can reduce cutaneous immunological inflammation. Atrophy of the skin, striae, telangiectasia, acneiform eruptions, steroid dermatitis, hypertrichosis, and other steroid adverse effects may occur with prolonged use. Treatment is more effective on the face, neck, and trunk, but fails miserably on the acral areas and the lips [9].

2. Calcineurin inhibitors:

The drug's action is to decrease inflammation by suppressing calcineurin, a protein that promotes inflammation by inducing IL-2 and tumour necrosis factor-α. A recent systematic review and meta-analysis found that topical calcineurin inhibitors perform similarly to topical steroids. Because they reduce the likelihood of skin atrophy, calcineurin inhibitors are more suited for use around the eyes, face, and neck [10].

The most significant issue is the increased likelihood of developing acne and herpes infections, as well as a burning or itching sensation. Multiple investigations have demonstrated that calcineurin inhibitors enhance melanogenesis [5].

3. Vitamin D and its analogues:

For pigmentation problems, topical applications of vitamin D or its equivalents like calcipotriol or tacalcitol are frequently utilised [11].

B) Systemic :

1. Corticosteroids:

To stabilise the condition and stop its progression, patients with fast advancing vitiligo should take oral mini-pulse (OMP) systemic steroids for 3-6 months at a dose of 0.1 mg/kg/day, taken twice weekly. After one to three months, the disease should stop spreading [5].Vitiligo patients have elevated amounts of CD4+ and CD8+ T cells in their peripheral blood and blocking NF-κB accelerates their death. Corticosteroids also reduce antibody production [12].

2. Azathioprine (AZA);

Research on azathioprine's (AZA) effectiveness in treating vitiligo has grown in recent years [13]. Conversion of AZA to 6-mercaptopurine, the active metabolite, occurs. 6-MP blocks the synthesis of DNA and RNA by reducing the rate of de novo purine synthesis. Additionally, AZA inhibits the synthesis of interleukin-2 (IL-2) which in turn decreases lymphocyte proliferation [14].

3.Methotrexate:

When corticosteroids aren't an option, methotrexate (MTX) may be a good substitute. Some research suggests that low-dose MTX may have anti-inflammatory effects by increasing levels of extracellular adenosine. Adenosine inhibits the synthesis of inflammatory cytokines such as TNF-α, IFN-γ, and IL-6 through a signalling cascade that occurs downstream [15].In the development of vitiligo, these cytokines are crucial. On the other

hand, MTX at high doses can inhibit cell proliferation and even cause activated CD4+ T cells to die off [15].

4.Cyclosporine:

The effectiveness of oral cyclosporine in treating vitiligo was investigated in three trials, two of which were pilot studies. These trials looked at the drug's effects on calcineurin-mediated activation of nuclear factor activated T cells and transcription of cytokine genes, such as IL-2, which is crucial for antigen-presenting cell function [13].

5.Minocycline:

An anti-inflammatory and immunomodulatory tetracycline antibiotic, minocycline is a versatile medicine. It shows promise as a treatment for vitiligo because it protects melanocytes from oxidative damage. By directly scavenging reactive oxygen species (ROS), it increases the viability of melanocytes and reduces ROS-induced apoptosis. This is the mechanism by which it exerts its antioxidant function [16].

6.Oral antioxidant agents:

A number of substances have been studied for their potential to treat vitiligo, including alpha-lipoic acid (ALA), gingko biloba extract (GBE), and polypodium leucotomos (PL) [13].

Biologics/immunomodulators:

1. **JAK inhibitors:**

Because many cytokines exert their effects via the JAK-STAT pathway, the most recently identified JAK inhibitors utilised to treat vitiligo are tofacitinib and ruxolitinib [5].

a) Tofacitinib:

Topical tofacitinib has also shown some success in treating vitiligo, and oral tofacitinib is a selective inhibitor of JAK1 and JAK3. It was initially administered to a female patient whose progressive disease had not responded to phototherapy or topical immunosuppressants such as calcineurin inhibitors or corticosteroids [17].

b) Ruxolitinib:

Ruxolitinib specifically inhibits JAK1 and JAK2 molecules, in contrast to tofacitinib [13]. An oral ruxolitinib treatment resulted in fast skin repigmentation and considerable reductions in serum CXCL10 levels in a male patient with vitiligo and AA, according to a case report published by Harris et al. [18]. The results of this study suggest that ruxolitinib has a role in blocking the IFN-y signalling and CXCL10/CRC3 axis. The first and only JAKi therapy for nonsegmental vitiligo in patients aged 12 and up is topical ruxolitinib, according to the FDA [5].

2. **TNF alpha inhibitors:**

While the precise way it works is still mostly unclear, it has been proposed that TNF-α, which is released by lymphocytes, triggers the production of IFN-γ, a protein crucial to the depigmentation process in vitiligo. Furthermore, in-vitro investigations demonstrated that TNF- α can, in a dose-dependent way, impede the repigmentation process by reducing melanocyte proliferation and tyrosinase activity expression. Research findings support the idea of looking at TNF-α as a possible target for treating vitiligo [13].

II. Phototherapy:

In vitiligo, phototherapy serves a dual therapeutic purpose by suppressing the immune system and stimulating melanocyte activity; it is a safe and effective treatment with several clinical uses [19]. Activated disease development can be halted by phototherapy, which causes T-cell death, downregulation of inflammatory cytokines, and overexpression of interleukin 10. Also, fewer antigen-presenting epidermal Langerhans cells are present [19].It causes keratinocytes to secrete basic fibroblast growth factor and endothelin-1, which in turn promotes melanocyte migration and proliferation from hair follicles to the epidermis [20].It appears that oxidative stress-induced damage is a component of vitiligo, and NB-UVB phototherapy may alleviate this damage in addition to the therapeutic advantages already mentioned in the treatment of the condition. Consequently, NB-UVB has emerged as the gold standard and phototherapy mode of choice for vitiligo [19]. Patients with resistant vitiligo or higher Fitzpatrick skin phototypes are among the unique cases when PUVA phototherapy is currently being considered [21].Contraindications of UVB include Patients' incapacity to adhere to safety protocols, a history of xeroderma pigmentosa or Gorlin syndrome, lupus erythematous [22].

Relative contraindications consist of a patient's inability to stand for lengthy durations or claustrophobia, a personal or familial history of skin cancer, and a history of exposure to ionising radiation or arsenic [22].Xerosis, moderate burning or discomfort, blistering, erythema, and itching are the primary acute side effects of NB-UVB [20].

Although there is little to no evidence that NB-UVB phototherapy causes cancer, the cumulative DNA damage that causes freckling and photoaging—including ocular photoaging—is a major cause for concern [20].

Excimer Light/LASER:

The Xenon chloride excimer laser/light (EL) therapy was initially described in 2001 for the treatment of vitiligo and received FDA approval in 2007. It uses a combination of noble gas (xenon) and reactive gas to emit monochromatic and coherent light with a wavelength of 308 nanometers (nm), which is adjacent to 311 nanometers narrowband-UVB (NB-UVB) (chlorine) [23].

Because of their shared properties and the fact that they both produce monochromatic light at a wavelength of 308 nm, lasers and light were regarded as a single therapy option [23]. Similar to NBUVB, it causes photobiological effects; however, EL provides more fluence to the depigmented lesions while avoiding the surrounding skin. Clinical trials have demonstrated that EL treatment outperforms NBUVB phototherapy in terms of clinical outcomes [24]. The benefit of this treatment is that it does not impact the surrounding skin and is recommended for areas of the body with less than 10% pigmentation [25].

Mechanism of action of Excimer light/Laser:

When subjected to a powerful electric current, the xenon and chloride gas mixture used by the dermatologic excimer laser forms unstable dimers. The "excited dimers" will split apart and release a coherent laser beam with a monochromatic wavelength of 308 nanometres [26].

Light at 308 nm produces DNA damage in keratinocytes and T lymphocytes, which decreases inflammation in T lymphocytes and proliferation in keratinocytes. This, in turn, causes apoptosis and cell cycle arrest by upregulating the p53 tumour suppressor pathway and downregulating the Bcl-2 proto-oncogene [27].

Excimer lasers are believed to promote repigmentation in disorders of depigmentation and hypopigmentation by activating and migrating melanocytes and increasing their production of melanin. UVB stimulates the proliferation of melanocytes and their migration from hair follicles to the epidermis, and this may explain why excimer lasers are more effective than NBUVBs [26].

The clinical response to excimer light is strongly correlated with the expression of c-kit+ (SCF receptor, CD117) in vitiliginous epidermis, as demonstrated by Park et al. [28]. During phototherapy, mitogenesis and the migration of melanocytes have been linked to several cytokines, such as stem cell factor, α-melanocyte stimulating hormone, and endothelin-1.

Irradiation causes inflammatory cells to die off and reduces levels of cytokines and mediators of inflammation. Additionally, it enhances melanocyte migration, proliferation, and melanogenesis by increasing the production of endothelin 1 from keratinocytes [26].

The photobiological effects are similar to those of NBUVB, and both light and lasers produce identical 308-nm monochromatic light. However, EL delivers more fluence to the depigmented lesions while sparing the uninvolved skin, and clinical trials have demonstrated that EL treatment produces better clinical outcomes than NBUVB phototherapy. The benefit of this treatment is that it does not impact the surrounding skin and is recommended for areas of the body with less than 10% pigmentation [24].

II. Surgical therapies:

Because they can be utilised in circumstances where other therapies have failed, surgical procedures are the most important tool for treating stable vitiligo [8]. Two subspecialties of surgical vitiligo treatment exist: cellular grafting and tissue grafting. Cellular grafting often involves suction blister epidermal grafting (SBEG) or mini-punch grafting (MPG), while tissue grafting often involves epidermal cell suspension (ECS) or follicular cell suspension (FCS) [29].

Methods were ranked from most effective to least effective. Topical therapies are the first-line options (corticosteroids and calcineurin inhibitors). Phototherapy with NB-UVB, psoralen, and UVA (PUVA) is the second line of defence, followed by systemic steroid treatment. Surgical grafting techniques make up the third line of treatment, and depigmenting treatments make up the fourth line. A comprehensive algorithm that provides a synopsis of the treatment options and a sequential plan is shown in Figure 1 [30].

Conclusions

Because vitiligo is recurrent and the rate of clinical progress is not always consistent, treating the condition can be frustrating at times. Treatment plans should be tailored to each patient's unique vitiligo condition, level of activity, and drug's potential side effects. No current treatment for vitiligo has the potential to reliably restore pigmentation in every patient. Phototherapy, surgical intervention, oral and topical immunosuppresants are common methods of management. Traditional treatments, on the other hand, are notoriously ineffective and accompanied by unpleasant side effects and a high relapse rate. To gain a better understanding of the

pathophysiology of vitiligo and to identify new therapeutic targets, additional research, both scientific and clinical, is necessary.

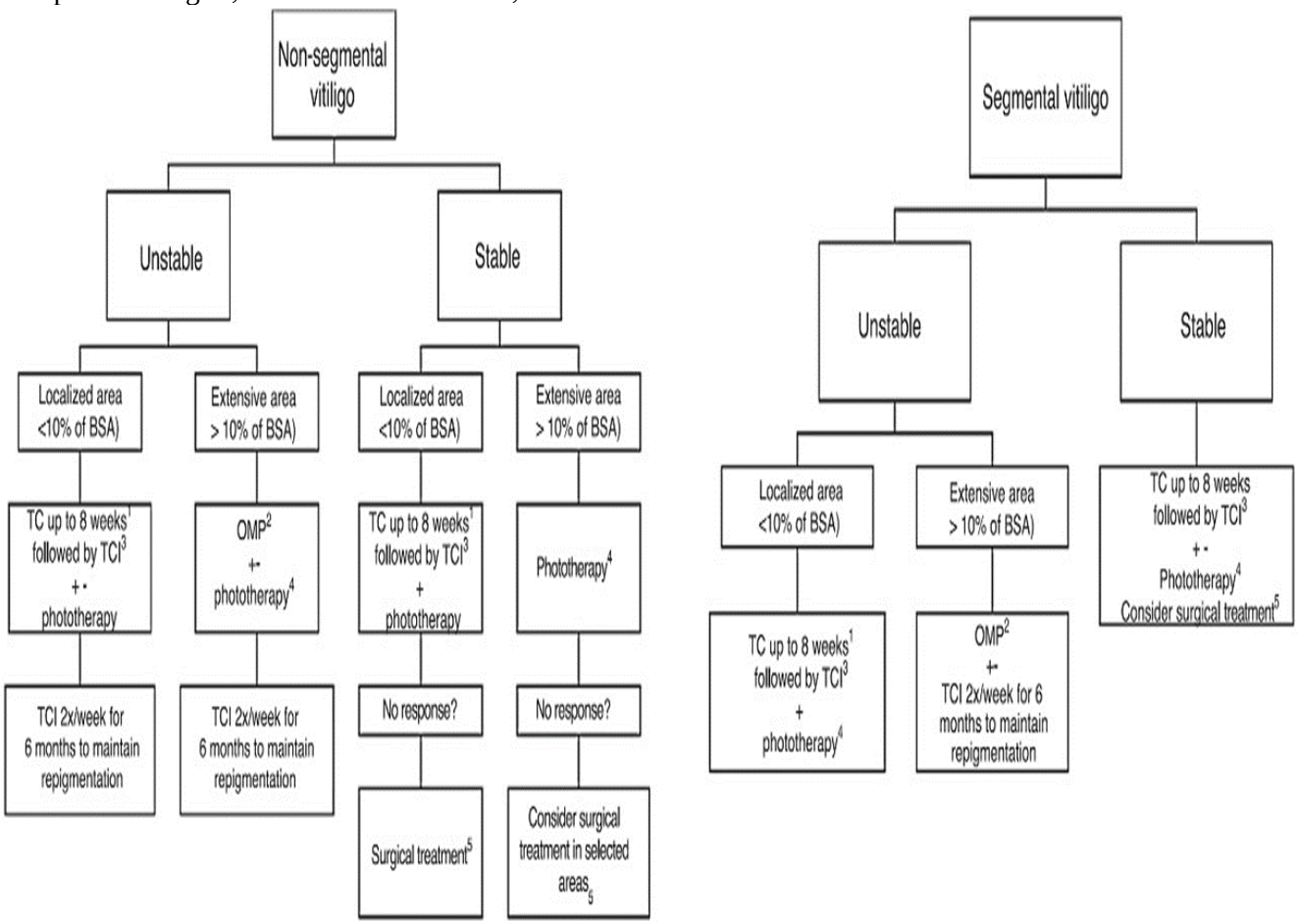

Figure (1): Therapeutic algorithm of vitiligo. Flowchart of treatment.

BSA, Body Surface Area; TC, Topical corticoid; TCI, Topical Calcineurin Inhibitor (Tacrolimus or Pimecrolimus); OMP, Oral Corticoid Mini-pulse.+-, Associated or not to.

1. With clinical monitoring to evaluate local side effects, especially if in genital, facial or skinfold areas. Most reviewers agree that, if the use of TC is necessary, preference should be given to those with low and medium potency in genital, skinfold and facial areas. The use of high and very-high potency corticosteroids should be restricted to the other body areas. Also, in sensitive areas, the use of TCI can be prioritized to minimize the side effects of topical corticosteroids.
2. In children and the elderly, evaluate the risk-benefit of using oral corticosteroid therapy, mainly due to the association between its use and growth deficit and increased fracture risk, in addition to comorbidities that can be triggered or aggravated by the medication use.
3. Tacrolimus (or Pimecrolimus) 2×/day.
4. Preferably NB-UVB, Excimer laser or Excimer light. Due to slow responders, a treatment lasting at least six months (2 to 3 weekly sessions) is suggested. In localized cases, give preference to phototherapy treatment that allows irradiation restricted to the lesion area. The association with oral anti-oxidants, TCI and TC during treatment can be considered. It was a consensus among the reviewers that the genital area should not be irradiated.
5. In the absence of Köbner phenomenon. [30].

Conflict of interest:

The authors declare no conflict of interest.

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