CHAPTER 4
Medical treatment of vitiligo

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Individuals affected by vitiligo have a vast reduction of quality of life. The color contrast between healthy pigmented skin and the depigmented vitiligo patches can give patients psychological problems [1,2]. Although up to now no treatment provides truly satisfactory results, physicians have a large variety of therapeutic approaches, both medical (including depigmenting therapies and camouflaging) and surgical [3]. This chapter will focus on medical treatment of vitiligo. A meta-analysis of the literature has shown that the best non-surgical therapies for localized and generalized vitiligo are topical corticosteroids and phototherapy, respectively [4]. However, comparison of all of the studies must be undertaken carefully, as great variability is apparent in the patient population (particularly localization, age, and skin type) and in the duration of treatment. New medical therapeutic approaches are also discussed.

Phototherapy

Phototherapy is considered one of the most effective treatments for vitiligo [5]. Several strategies are used including ultraviolet A (UVA) phototherapy, photochemotherapy (oral and topical) such as psoralen plus UVA (PUVA), psoralen plus sunlight (PUVASOL), broad- and narrowband UVB (BB- and NB-UVB, respectively) phototherapy, 308-nm excimer light and combination phototherapy.

There is increasing evidence that UVB therapy is superior to UVA in treating vitiligo. Many studies have demonstrated the effectiveness of PUVA therapy in this indication; however, there are specific contraindications and a higher risk of side effects, including skin carcinomas, associated with it [6–9]. It is important to note that long-term follow-up of UVB therapy is much more limited than UVA, but,

by means of a dose–response model, it has been calculated that long-term NB-UVB therapy may carry substantially less risk for skin cancer than PUVA therapy [10].

UVA phototherapy

Topical PUVA (paint) photochemotherapy

Most investigators agree that topical psoralen photochemotherapy should be restricted to vitiligo patients with an involvement of less than 20% of the body surface. This treatment can be used in children. Topical PUVA is difficult to perform because of the high risk of phototoxicity from the topical psoralen formulations. However, advantages of topical PUVA include lower cumulative UVA doses than oral PUVA and lack of ocular and systemic toxicity. Low concentrations of psoralens should be used. A 0.1% concentration of 8-methoxypsoralen (8-MOP) has the same effectiveness as higher concentrations (0.5% or 1%), but a lower risk of toxicity. The commercially available 1% 8-MOP lotion should be diluted from 1:10 to 1:100. The patient should be exposed to UVA approximately 20–30 minutes after application of the topical preparation (preferentially cream or ointment to avoid "running" leading to streaks of hyperpigmentation) with a cotton-tipped applicator by a physician or a nurse to avoid a rim of hyperpigmentation around the lesions if the psoralen is applied on the surrounding normally pigmented skin. The initial dose should not exceed 0.25 J/cm^2. This treatment is performed once or twice a week, never on consecutive days with increments by $0.12–0.25 \text{ J/cm}^2$/week, until mild erythema is achieved at the treated sites. Following treatment, the area is washed, a broad-spectrum sunscreen is

applied, and excessive sun exposure is avoided for at least 24 hours [11].

The mean clinical response is about 60% repigmentation, depending on the anatomic site. Due to the risk of severe blistering reactions, topical photochemotherapy should never be used with sunlight as an UVA source. However, a home topical PUVA protocol using very dilute 8-MOP (0.001%) has been proposed for the treatment of vitiligo. In a large cohort of patients ($n = 125$), only 3% had blistering reactions [12].

Oral PUVA photochemotherapy

PUVA involves the use of psoralens followed by exposure to long-wavelength UVA irradiation. Oral PUVA is used most commonly in patients with extensive vitiligo.

There are numerous psoralens occurring naturally in plant species. Of these, only a few are used therapeutically, including methoxsalen (8-MOP), trioxsalen (4,5′,8-trimethylpsoralen), and bergapten (5-MOP), almost exclusively for vitiligo. Trioxsalen is no longer available and 5-MOP is pending approval in the USA.

By far the most commonly used oral psoralen is 8-MOP (0.4–0.6 mg/kg) and treatments are typically administered 2 times/week. For patients with vitiligo, the initial dose of UVA is usually 0.5–1.0 J/cm^2. This dose is gradually increased until minimal asymptomatic erythema of the involved skin occurs. 5-MOP has about the same response rate as 8-MOP in repigmenting vitiligo. The former appears to be more suitable for the treatment of vitiligo because of its lower incidence of adverse effects, in particular a reduced phototoxicity of depigmented skin as well as less nausea and vomiting.

The response rate of PUVA is variable, and complete repigmentation is achieved in only a few patients. Some degree of repigmentation is seen in about 60–80% of patients. A satisfactory cosmetic result is usually obtained in less than 20% of cases. According to a recent meta-analysis, the mean success rate in treating vitiligo for oral methoxsalen plus UVA was 51%. As with other forms of phototherapy and topical corticosteroids, the areas that respond most favorably are the face, the mid-extremities, and the trunk [4]. The total number of PUVA treatments

required is between 50 and 300. Evidence of repigmentation is usually first seen after 1–4 months of treatment, but complete repigmentation usually requires 100–300 treatments. Repigmentation, as with NB-UVB, usually appears in a perifollicular pattern and/or from the periphery of the lesions. The former represents the repopulation of the interfollicular epidermis with melanocytes from the follicular reservoir, and pigmented hairs are a better prognostic sign than depigmented hairs. General contraindications to oral PUVA include photosensitivity disorders during pregnancy and lactation, a history of skin cancer, arsenic exposure or cutaneous radiation therapy, cataract and retinal disease. To date, only a few vitiligo patients with PUVA-induced cutaneous carcinomas have been reported. This may reflect a smaller cumulative UVA dose, but large follow-up studies have not yet been done in PUVA-treated vitiligo patients. Until more data are available, it seems wise to recommend a maximum cumulative PUVA dose and a maximum number of UVB treatments of 1000 J/cm^2 and 300 treatments, respectively, to vitiligo patients.

The rate of repigmentation with oral PUVA varies, depending upon the anatomic site. Schematically two groups of lesions can be identified:

1 the UV-responsive lesions that include the face and neck, the trunk, and the proximal extremities;
2 the UV-resistant areas, including the bony prominences, the distal digits, and the lips.

Children with vitiligo tend to respond somewhat better to PUVA than adults. Darkly pigmented patients often achieve more repigmentation with PUVA than patients with lighter skin, probably because they tolerate higher UVA doses.

Retention of PUVA-induced repigmentation has been observed in more than 90% of patients, 14–15 years after discontinuation of treatment. Retention of repigmentation seems to be more common in areas with complete repigmentation.

UVB phototherapy

BB-UVB

Very few studies to evaluate the potential of BB-UVB in the treatment of vitiligo are available. One of the studies reported that 75% repigmentation

was achieved in 8 of 14 patients after 12 months of treatment, mostly in patients with skin phototypes IV–VI [13]. These results are not confirmed by a recent intra-individual comparative study, which showed 22% of patients treated by NB-UVB achieved a repigmentation of at least 75% after 12 months of treatment versus none with BB-UVB [14]. The latter study involved only 10 patients, and the localization of the treated lesions was different between the two groups (upper part of the body for NB-UVB and lower part for broadband). Larger studies are still needed but NB-UVB should be preferred to BB-UVB in treating vitiligo.

PUVB (with BB-UVB)

A left–right comparative study suggests that PUVB is equally effective as PUVA therapy [15] in the treatment of vitiligo. Each patient received 0.7 mg/kg 8-MOP 2 hours before session. BB-UVB initial dose of 0.03 J/cm^2 was increased by 0.03 J/cm^2 every session whereas UVA was started at 0.5 J/cm^2 and increased by 0.5 J/cm^2 every session. All the patients were skin types III and IV. After 30 sessions, both PUVA and PUVB produced 50–60% of repigmentation with similar incidences of side effects.

Unfortunately, no comparative study of PUVB versus UVB monotherapy is yet available.

NB-UVB

Narrowband fluorescent tubes (Philips TL01/ Waldman) with an emission spectrum of 311 nm are used for this therapy. A meta-analysis of the literature concludes that NB-UVB therapy is the most effective and safe therapy for generalized vitiligo [4]. The starting dose varies from 100 to 250 mJ/cm^2, with increments of 10–20% at each subsequent exposure and then held once a mild erythema develops. Treatments are administered 2–3 times/week, never on 2 consecutive days. Several studies have demonstrated the effectiveness of NB-UVB as monotherapy. About 60% of patients obtain greater than 75% repigmentation. Short-term side effects include pruritus and xerosis. Long-term side effects are unknown. The advantages of NB-UVB over oral PUVA include shorter treatment times, no drug cost, no or less side effects such as nausea, phototoxic reactions. There is no need for post-treatment

photoprotection. This treatment can be used in children, pregnant or lactating women, and in individuals with hepatic and kidney dysfunctions. Furthermore, there is less contrast between depigmented and normally pigmented skin, and possibly less long-term side effects. NB-UVB therapy is becoming the first choice of therapy for adults and for children (over 6 years of age) with vitiligo [16].

NB-UVB has been used in combination with pseudocatalase. However, no controlled studies have been performed to validate the beneficial effect of adjuncting pseudocatalase [17].

Focused micro-phototherapy

In the past few years new devices delivering UVB light have been developed for the treatment of localized vitiligo. NB-UVB micro-phototherapy utilizes a device that delivers a focused beam with spectrum from 300 to 320 nm with a peak emission of 311 nm. Two studies report excellent results [18,19], but comparative studies with 308-nm excimer laser are still lacking. Monochromatic excimer light 308 nm can also be delivered by lamps. A pilot study using such a device reports that 18 out of 37 vitiligo patients achieved 75% or more repigmentation after 6 months of treatment. These observations should be confirmed by a comparative trial (excimer laser versus excimer lamp), in a larger population [20].

Other photochemotherapies

Khellin (topical or systemic) plus UVA (KUVA) or phenylalanine plus UVA have also been proposed for the treatment of vitiligo. There have been conflicting reports regarding these treatment strategies, and there is a concern about the hepatic toxicity of khellin. For these reasons, these modalities are not recommended for the treatment of vitiligo.

Immunomodulators

In the recent past, several preliminary studies have reported the efficacy of immunomodulatory drugs, including levamisole, anapsos, isoprinosine, and suplatast, as repigmenting agents for the treatment of vitiligo. Unfortunately, none of these initial observations have been followed by clinical studies

demonstrating the efficacy of these compounds in the treatment of vitiligo. As a consequence, these agents have not been widely used by vitiligo patients. However, recent advances in vitiligo research provide information strengthening the autoimmune theory of vitiligo. Corticosteroids and topical immunomodulators, such as tacrolimus, demonstrate some efficacy for the treatment of vitiligo.

Corticosteroids

Topical steroids are useful for the treatment of localized vitiligo. Marked or almost complete repigmentation can be obtained with potent corticosteroids (e.g. betamethasone valerate, fluticasone propionate) and very potent corticosteroids (e.g. clobetasol, betamethasone). However, corticosteroids of low pot-ency show no therapeutic effect at all. A recent meta-analysis concluded that potent and super-potent topical steroids are effective treatment for localized vitiligo [4].

Steroid-induced repigmentation occurs within 1–4 months of treatment in a perifollicular pattern and from the margins of the lesions. Side effects include dermal atrophy, steroid-induced acne, rosacea, telangiectasia, ecchymoses, and striae. Furthermore, suppression of the hypothalamic–pituitary–adrenal axis may occur after prolonged applications on large areas. To minimize the incidence of these side effects, it is recommended to use topical steroids on limited skin areas, to avoid prolonged use on "sensitive" areas such as face and body folds, and to use them once or twice daily for only 6–8 weeks followed by a treatment-free interval of several weeks as mild steroid-induced skin atrophy is reversible. No repigmentation after 3 months of treatment should lead to discontinuation of treatment. The mechanism of steroid-induced repigmentation is unknown, although several hypotheses are proposed: suppression of immunity-driven melanocyte destruction? Stimulation of melanocyte proliferation and migration?

Intra-lesional corticosteroids must be avoided.

Systemic steroids (high-dose pulsed therapy, minipulsed regimen, or daily oral low-dose) have been claimed to rapidly arrest spreading vitiligo and induce repigmentation. In most of these studies, a response to systemic corticosteroid therapy has been limited to patients with rapidly progressive generalized vitiligo. Given the significant potential for serious side effects of systemic corticosteroid therapy, the role of these drugs in the treatment of vitiligo remains controversial. We do not recommend this therapy for vitiligo patients.

Calcineurin inhibitors

Preliminary observations suggest that tacrolimus and pimecrolimus may be effective treatments for both localized and generalized vitiligo [21,22]; 0.1% tacrolimus ointment is applied twice daily for about 3 months [23]. Unfortunately, these studies are open label involving a very small number of patients.

A 2-month double-blind randomized trial compared 0.1% tacrolimus and 0.05% clobetasol propionate in children with vitiligo [24]. This study confirmed the initial observation that tacrolimus stimulates vitiligo repigmentation however tacrolimus ointment was not superior to clobetasol in terms of repigmentation. The same results were recently obtained in an open intra-individual study performed with 1% pimecrolimus cream [25]. Once again 0.05% clobetasol propionate induces comparable rate of repigmentation as that with topical calcineurin inhibitor. Interestingly enough the best results were observed on sun-exposed areas suggesting that UV may also be involved in tacrolimus- and pimecrolimus-induced repigmentation of vitiligo. Further studies are required to establish the safety and efficacy of topical calcineurin inhibitors in the treatment of vitiligo. Recent personal observations suggest that tacrolimus monotherapy in the absence of UV has little or no repigmenting potential in vitiligo [26].

Combination therapies

Interest in combination treatments was first clearly demonstrated with the combination of UVA and topical steroids. In this prospective, randomized, controlled, left–right comparison study, it was shown that the combination of UVA and fluticasone propionate was much more effective than UVA or topical steroid alone [27]. To the best of our knowledge, the combination of UVB therapy with topical steroids

has not yet been evaluated, although some series have studied the combination of UVB and other synergistic drugs.

Oxidative stress has been shown to be involved in the pathogenesis of vitiligo. Pseudocatalase has the ability to remove hydrogen peroxide and so could be interesting in the treatment of vitiligo. The combination of topical pseudocatalase with UVB has shown very promising results in a pilot study (complete repigmentation on the face and the dorsum of the hands in 90% of patients) [17]. Unfortunately, these results were not confirmed in a later study [28].

The occurrence of repigmentation of vitiligo in patients treated with calcipotriol (a vitamin D3 analog) for psoriasis has suggested that it might be efficacious in treating vitiligo. The use of calcipotriol with sun or PUVA therapy has provided some interesting rates of repigmentation. However, the results are very controversial [29–31]. Combination of calcipotriol and UVB also provides controversial data. However, two of the three studies clearly showed that the combination of calcipotriol with UVB had no enhancing effect on repigmentation suggesting the absence of interest of adding calcipotriol to UV [14,32,33].

Tacrolimus ointment has shown some interesting results in the treatment of vitiligo, but the best results were achieved in sun-exposed areas. So far, two studies have evaluated whether the combination of 308-nm excimer laser and topical tacrolimus could be synergistic. These series have compared the efficiency of 308-nm excimer combined with tacrolimus ointment to 308-nm excimer laser monotherapy [34] or associated with placebo ointment [35]. In both cases, a total of 24 sessions were done and tacrolimus ointment was applied twice a day. The results were similar and showed a greater efficiency with the combined treatment as compared to laser alone. Tolerance was good and side effects were limited to constant erythema, sticking, and rarely bullous lesions. These encouraging results are corroborated by two others reports associating UVB light and topical tacrolimus [36,37]. However, the increased risk of skin cancers promoted by combining of two immunosuppressive treatments cannot be excluded. So, pending a long-term follow-up, this combination should be reserved to control studies.

Others

Systemic antioxidant therapy

The rationale for this approach rests on the hypothesis that vitiligo results from a deficiency of natural antioxidant mechanisms. Although to date not validated by a controlled clinical trial, selenium methionine, tocopherols, ascorbic acid, and ubiquinone are widely prescribed by dermatologists to arrest spreading of vitiligo and to promote its repigmentation.

Topical calcipotriol

Topical calcipotriol as monotherapy has no effect on vitiligo.

Prostaglandin

Prostaglandin has been shown to play a role in melanocytes proliferation and melanogenesis. A pilot study has evaluated the topical applications of prostaglandin E2 (PGE2) in treating localized vitiligo [38]. After 6 months of daily applications, 15 of 24 patients achieved marked to complete repigmentation. Side effects were limited to mild irritation in two cases. However, these encouraging results have not been confirmed so far.

Depigmentation therapies

Patients who have widespread disease with only few areas of normally pigmented skin on the face or other exposed areas can be treated with depigmenting agents. The patients must be carefully chosen: adults who recognize that their appearance will be altered significantly and who understand that depigmentation also requires lifelong care of the skin (sunscreens, protective clothing, etc.).

The guidelines for using permanent depigmentation in vitiligo are as follows [39]:
1 Desire of permanent depigmentation
2 Age over 40 years
3 More than 50% of depigmentation of the sites to be treated
4 Willingness to accept the fact that repigmentation will no longer be possible

A psychological evaluation of the readiness of patients undergoing such as full skin bleaching is highly desirable. Previous studies have demonstrated such a procedure as valuable [40].

The most commonly used agent for further depigmenting vitiligo patients with an extensive involvement is monobenzylether of hydroquinone (MBEH) 20% applied twice daily to the affected areas for 9–12 months or more. MBEH is a potent irritant and/or allergenic compound. A patch-test to detect contact sensitivity to MBEH should be performed before starting therapy. It normally takes 1–3 months to initiate a response. Loss of pigment can also occur at distant sites of applications. Although depigmentation from MBEH is considered as permanent, repigmentation following a sunburn or even intense sun exposure may occur. Monomethylether of hydroquinone (MMEH) also named 4-hydroxyanisole or 4-methoxyphenol in a 20% cream can be used as an alternative for MBEH. Side effects include contact dermatitis, pruritus, exogenous ochronosis, and leukomelanoderma en confetti. Depigmentation by Q-switched ruby laser therapy is reported to achieve faster depigmentation compared with depigmentation using a bleaching agent [41].

Photoprotection

Photoprotection may be useful to prevent sunburn of susceptible vitiligo skin or induction of Köbner phenomenon. Furthermore, sun exposure stimulates tanning of uninvolved skin and increases the contrast with lesional skin. On the other hand, sun exposure can promote repigmentation of vitiligo.

Sun block preparations containing zinc oxide or titanium dioxide are claimed to be more effective than other sunscreen preparations. However, the new broad-spectrum sunscreens providing both UVA and UVB protection are very efficient provided they are reapplied every 2 hours. Use of sun-protective clothing such as wide-brimmed hats should also be recommended.

Camouflaging

The goal of camouflage is to normalize the appearance of a patient suffering from a disfigurement. This is usually done on lesions in the exposed areas, such as the face and the dorsal regions of the hands. This approach is very interesting in areas resistant to medical and surgical treatments such as the extremities of hand and feet. A recent study demonstrates that cosmetic camouflage advice improves quality of life in patients with vitiligo [42]. Unlike traditional cosmetics, cover creams are used because of their unique properties. They are waterproof and opaque and offer wide varieties of cosmetic shades. Corrective cosmetics are available in various shades, allowing a perfect match to normal skin color in most patients. Synthetic melanins have been incorporated into cover-ups that may be useful in patients with vitiligo [43].

The use of DHA (dihydroxyacetone 1,3-dihydroxydimethylacetone) to camouflage the depigmented lesions of patients with vitiligo vulgaris and segmental vitiligo has been proposed recently [44]. DHA preparations color the stratum corneum brown owing to its oxidative properties and provide temporary pigmentation resembling a UV-induced tan. In general, DHA pigmentation is not considered to be photoprotective. Recent investigations suggest that manipulation of the extent of hydration, pH, and availability of certain amino acids in the stratum corneum might produce DHA-induced pigmentation with greater photoprotection. For the camouflage of vitiligo lesions, DHA was stabilized at optimal levels. Five percent DHA was prepared with 10% ethanol and 1% sodium citrate buffer with 0.1% ethylene diamine tetracetic acid (EDTA) at pH 4.5 at 4°C. After application with a sponge swab, the result appeared after a reaction time of approximately 6 hours. The pigmentation cannot be rubbed off on clothes or be removed by washing and remains for about 3–4 days. The color fades slowly with desquamation of skin. The main disadvantage is that it does not give a uniform color to the skin.

Beta-carotene and canthaxanthin (Phenoro-β-carotene 10 mg and canthaxanthin 15 mg per capsule) oral preparations have been used to treat cosmetic defects in vitiligo. By darkening vitiliginous skin, they reduce the contrast between involved and normally pigmented skin. Good cosmetic results are seen in vitiligo patients with skin types I and II. In one study, 10–35% of patients gave very satisfactory responses, with the rest unsatisfactory. There is increased resistance to sun exposure in vitiligo. As canthaxanthin is reported to produce retinopathy, proper ophthalmic consultations are mandatory.

Eye shadows, mascaras, and liners accentuate patients' eyes and draw attention to them to further distract from facial cosmetic defects while lipsticks can be used to cover vitiligo of lips.

Psychological support

Vitiligo may cause a considerable level of distress due to its disfiguring nature and the quality of life of a majority of patients is very severe. Vitiligo patients often experience indifference from the doctors toward their skin problem and do not feel adequately supported by them. About 50% of the vitiligo patients feel that they are not adequately informed about their disease and its treatment [45]. Only 36% of physicians encourage their patients to treat disease, being pessimistic concerning expected treatment results [44].

Conclusion

Patients suffering from vitiligo need a global therapeutic approach. The disease and its course need to be fully explained to the patients and all therapeutic options discussed. Medical treatments bring very useful ways to repigment or decrease the contrast with healthy skin. Potent topical steroids and NB-UVB are considered to be the best first choices for localized and generalized vitiligo, respectively. However, treatments such as topical calcineurin inhibitors and focused phototherapy provide interesting new options. Finally, the combination therapies clearly show better rates of repigmentation and their use should certainly increase in the next few years.

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