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New and Experimental Treatments of Vitiligo and Other Hypomelanoses

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A wide range of disorders can present as cutaneous hypopigmentation, and this article is dedicated to the introduction of and discussion about the most recent and innovative researches in the treatment of vitiligo and other depigmenting disorders. It also provides a description of the newly developed techniques that are in the hands of dermatologists, dermato-cosmetologists, and dermatologic surgeons.

We cannot ignore the fact that among all the hypomelanoses, vitiligo is the most remarkable and challenging and that almost all the research and innovations made in the field of hypopigmentation treatment are caused by the continuous efforts to reach the ultimate therapy for vitiligo. We must be fully aware that not all hypopigmentation disorders respond in the same way to the different treatment modalities. Several hypomelanoses are reversible and do not require any treatment. In contrast, therapy of permanent hypomelanoses is difficult and often unsuccessful. Multiple treatment options are available for depigmentation caused by vitiligo, whereas the treatment of leukoderma in disorders such as nevus depigmentosus, hypomelanosis of Ito, tuberous sclerosis, and piebaldism is limited. Because of their inflammatory etiology, postinflammatory hypopigmentations may be well treated with classical approaches (eg, topical corticosteroids and phototherapy). Conversely, disorders such as oculocutaneous albinism are not currently capable of undergoing repigmentation therapy.

New treatments for hypomelanoses

In recent years, the interest in vitiligo, among all the other hypopigmentation disorders, is increasing, partly because of the aesthetic challenge represented by the disease itself and partly as a reaction to the intolerable discrimination against the affected subjects. Vitiligo is not an unmanageable disease, and many studies on new therapeutic protocols showed a relevant efficacy, even if we are far from the ultimate therapy [1]. This interest in vitiligo has the effect of discovering alternative and, in some cases, more efficient treatment modalities to be used in other primitive or secondary hypomelanoses, such as piebaldism, pityriasis alba, posttraumatic and postinfectious hypopigmentation, and chemical leukoderma, melanoma-associated leukoderma.

These treatments should have the aim of resetting completely the appearance and function of the healthy skin. Melanocytes usually respond slowly to the different treatments, so it could take several months to reach acceptable results in term of repigmentation. Affected subjects must be aware of this process and acquiesce with the possibility of a long-term therapy. Newly available treatments for hypopigmentation are medical, physical, and surgical, alone or in association (Box 1).

Ultraviolet B narrow band

Although the precise biologic mechanisms stimulated by UV light in terms of effective repigmentation must be confirmed, the efficacy of UVB light in vitiligo is probably caused by the production of high levels of cis-urocanic acid, a metabolic product that causes cutaneous

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Box 1. Treatments for hypopigmentation

UVB narrow band
UVB narrow band microphototherapy
UVB narrow band excimer laser and monochromatic excimer light
Tacrolimus and pimecrolimus topicals
Pseudocatalase topicals
Derivatives of vitamin D topicals
Topical prostaglandin (PGE_2) analog
Cucumis melo extracts topicals
Surgical treatments
Treatment with tissue-engineered skin
Depigmentation therapy

immune suppression. Melanogenesis is thought to be stimulated by UVB radiation through the activation of nitric oxide-cGMP-proteinkinase G pathway, and/or by the activation of the cAMP-pathway by alpha-melanotropin, and/or through melanocyte-stimulating hormone receptor-binding activity and melanocortin receptor gene expression [2].

The first data on the use of UVB in the treatment of vitiligo (broadband UVB: 280–320 nm) appeared in 1990, whereas the first report on UVB narrow band (NB-UVB) therapy (NB-UVB: 311 ± 2 nm) appeared in 1997 [3]. This latter study showed that NB-UVB were more effective, compared with topical UVA treatment, in the treatment of vitiligo, with faster repigmentation and less contrast between normal and depigmented skin [3]. Subsequent meta-analysis on nonsurgical treatments for vitiligo showed that results obtained with UVB and NB-UVB therapy were almost the same as results obtained with psoralen plus Ultra Violet A (PUVA) [1]. A combination of UVB and other therapies, such as pseudocatalase, calcipotriol, and phenylalanine, was considered.

Treatment protocols vary in different studies, with an initial dose of irradiation ranging from 0.075 J/cm^2 to 0.25 J/cm^2 and increasing by 20% after each treatment until a slight erythema is reached. Cumulative doses are lower than in PUVA therapy, however. Stating the major advantages of avoiding psoralen side effects and low cumulative dose of radiation, evidence-based guidelines for the treatment of vitiligo indicate that NB-UVB phototherapy is recommended for generalized vitiligo [4]. UVB treatments can be safely used in pregnant women and children and are related to less erythema, no phototoxic effects, and no epidermal thickening after long-term irradiation. No statistical differences exist between PUVA, NB-UVB, or broadband UVB regarding success rates.

Ultraviolet B narrow band microphototherapy

This new therapeutic approach evolved from the consideration that vitiligo patients undergoing phototherapy were receiving a high cumulative dose of radiation during their lives, which led to secondary cutaneous disorders, such as photoaging, telangiectasias, and excessive tanning. These considerations led to the development of a new phototherapy device named BIOSKIN, which involved so-called ''microphototherapy'' [5]. Microphototherapy is based on a photo exposition limited to well-defined areas, and it avoids the collateral effects associated with diffuse phototherapy (eg, photoaging, erythema, and burns) [1,2,5–7]. It uses a narrow band UVB light (Philips TL-10) with a wavelength peak at 311 nm that is selectively delivered to the white patches. It enables drastic reduction of the total dose of radiation and the most common side effects related to the exposition to UV rays: excessive tanning of the nonaffected skin, photoaging, telangiectases, and the risk of neoplasms. It also avoids an increase in the chromatic contrast between normal and lesional skin. With this treatment, one can administer different doses of UVB radiation in different areas of the body (ie, the hands need more UVB than the eyelids to repigment), which optimizes the treatment by tailoring it to each subject.

The initial dose of radiation is 20% less than the minimum erythema dose, which is evaluated through the exposition of affected and unaffected skin to increasing doses of UVB (80, 160, 240, 320, 400 mW/cm^2) at least 3 days before the beginning of the treatment. During the following sessions, each patch is uniformly irradiated. In ''sensitive'' areas (eg, eyelids), 80% of minimum erythema doses are used. The radiation dose is increased by 20% at each session. When erythema occurs, the dose is lowered by 20% in the erythematous area only. Some skin areas can resist photostimulation better and are irradiated with higher regimens (up to twice the dose of the most sensitive areas). Sessions are repeated every 21 to 30 days until repigmentation is reached, which may take from 2 months to 2 years [2,6,7].

Partial repigmentation is often seen after at least three to six sessions (63% of the cases),

beginning just after 2 months of treatment as a pigment pitting around each follicular ostium (follicular repigmentation) usually accompanied by an evident interfollicular repigmentation. Photographic evaluation is useful to assess the clinical results, and Wood's light is used for lighter phototypes.

In a recent study, 734 patients were irradiated using this protocol every 2 weeks for 12 consecutive months [8]. At the end of the study period, 69.8% of patients ($n = 510$) achieved normal pigmentation on more than 75% of the treated areas, 21.12% ($n = 155$) achieved 50% to 75% repigmentation on the treated areas, and only 9.4% ($n = 69$) showed less than 50% repigmentation with no statistical significance between segmental and nonsegmental vitiligo. (In 5 patients in this group the vitiligo was aggravated.) The results of this study are similar to those obtained by total-body UVB irradiation in international studies, enriched by the advantages of fewer side effects.

Microphototherapy is particularly useful in patients affected by segmental vitiligo and bilateral symmetrical vitiligo in whom the total amount of body surface involved is less than 20%. The only side effect occasionally reported is transient erythema, rarely followed by desquamation [6]. Microphototherapy is not administered to patients who have actinic sensitivity (eg, systemic lupus erythematosus, xeroderma pigmentosum, porphyriasis, cutaneous viral infections) or patients treated with topical or systemic photosensitizing agents.

Ultraviolet B narrow band excimer laser and monochromatic excimer light

After the consistent results obtained by narrow band microphototherapy with light source devices such as BIOSKIN, another innovation—still experimental—was introduced: excimer laser therapy and monochromatic excimer light therapy with monochromatic UV rays at 308 nm. These therapies are not so different from the "classical" narrow band radiation. They are capable of selectively treating single hypopigmented patches and sparing nonaffected areas. A recent study analyzed the effects of excimer laser in 24 patients and reported total repigmentation in the treated areas in 12% of subjects ($n = 7$), partial (25%–75%) repigmentation in 25% ($n = 6$), less than 25% repigmentation in 25% of patients, and no results in 20.8% of patients ($n = 5$) [9]. The efficacy of the treatment seems to be related to treatment duration (ranging from 17–57 months of therapy in this study) and lower mean duration of the disease.

This technique, which is among the newest ones, should deserve further attention, and perhaps focus on the treatment of other diseases that occur with hypomelanosis. Similarly, monochromatic excimer light has shown similar positive effects in the repigmentation of vitiligo patches [5,10].

Recently introduced topical treatments

Low levels of catalase in the epidermis of patients who have vitiligo increase H_2O_2 levels, which inhibits 6-BH_4 metabolism and melanogenesis [11]. The use of creams containing pseudocatalases has been shown to stop vitiligo progression and induce repigmentation [12]. Pseudocatalase acts as a substitute for impaired levels of catalase, degrading excessive hydrogen peroxide and allowing recovery of enzyme activities. Narrow band UVB-activated topical pseudocatalase has been proposed for vitiligo treatment, but although some repigmentation has been observed in approximately 60% of patients treated with this modality, the degree of contribution of the UVB radiation to these results is not known [13].

Some authors report positive results after topical administration of tacrolimus ointment 0.1%, particularly on sun-exposed areas of the skin (eg, face and neck) [7,14]. Tacrolimus seems to work selectively by inhibiting T-lymphocyte activation, which blocks the production and secretion of proinflammatory cytokines, such as tumor necrosis factor-α, whose levels are increased in vitiligo skin but not in healthy controls [15]. This finding suggests that repigmentation could be partly associated with reduced levels of tumor necrosis factor-α in affected skin. The association of tacrolimus ointment with excimer laser 308 nm seems an effective treatment for vitiligo, but the possibility of unexpected sunburns must be considered [16]. Pimecrolimus cream seems similarly active in the treatment of vitiligo patches.

A recent approach to the treatment of vitiligo is based on the thought that UV ray–induced melanogenesis is partly caused by UV-induced turnover of membrane phospholipids that generate prostaglandins and other products, maybe representing the activating signal for repigmentation. Some authors observed in vitro enhancement

of melanogenesis by PGE_2, and in a recent study vitiligo patients with less than 5% skin involvement were treated with a topical a gel that contained 166.6 μg/g PGE_2 applied in the evening to depigmented skin for 6 months [17,18]. Of the 24 patients evaluated at the end of the study period, 15 reported marked (50%–75%) to complete repigmentation (6 focal vitiligo, 7 vitiligo vulgaris, 2 segmental vitiligo), whereas 6 patients showed 25% to 50% improvement and 6 showed minimal or no improvement. The observed side effects were episodes of mild irritation after exposure to sunlight. Although the exact mechanism of repigmentation is not clear, different mechanisms have been suggested, including (1) influencing melanocyte responsiveness to neuronal stimulation, (2) melanocyte proliferation, and (3) direct or second messenger-mediated interaction with melanocytes through the stimulation of tyrosinase activity. Other mechanisms that do not directly involve melanocytes have been proposed, but one of the most interesting focuses on the immunosuppressive role of in vitro and in vivo PGE_2 [17]. Other trials should be undertaken to evaluate the correct use of topical prostaglandin analogs in patients who have vitiligo.

Patients who have vitiligo exhibit reduced levels of intracellular calcium in keratinocytes and melanocytes [19]. The calcium decrease parallels increased thioredoxin levels, which could inhibit tyrosinase activity and melanogenesis. Derivatives of vitamin D act on melanocyte receptors for 1,25-dihidroxy-vitamin D, modifying the altered calcium homeostasis and permitting a more rapid repigmentation when used alone and when associated with classical PUVA treatment [20].

Cucumis melo extracts have shown relevant super-oxide-dismutase and catalase-like activities when associated with selective UVB therapy [21]. In vitro and experimental data show an interesting performance of this vegetable extract, which is well accepted by patients who have vitiligo and family members of children affected by the disease. Excellent results have been observed in association with focused UVB narrow band (BIOSKIN) treatment, which shows that the association represents a safe and effective treatment and is well tolerated and accepted by patients [22].

Surgical therapies

Autologous skin grafts are an option for repigmentation in a subset of patients who have stable vitiligo that is refractory or partially responsive to medical treatment and in patients who have piebaldism or persistent depigmentation caused by halo nevi, thermal burns, trauma, or inflammation. Surgical options are considered for patients who have vitiligo with areas of involvement more than 2 to 3 cm that contain depigmented hairs or involvement of sites such as the lips or fingers, which are unlikely to have a satisfactory response to medical therapy. It is mandatory that the disease be stable; stability is the most critical factor in the selection of patients with recalcitrant vitiligo as candidates for surgical repigmentation. Some authors suggest surgically treating vitiligo patches only if stable for at least 2 years and performing a minigrafting test before the graft to evaluate the positive response and the absence of koebnerization at the donor site after 2 to 3 months follow-up [6,23]. Active vitiligo has a higher risk for graft failure, recurrence of depigmentation, and koebnerization at the donor site [24]. Other important factors that affect graft outcome in patients who have vitiligo include the location and type of disease, with 95% success rates for test grafting in segmental or focal vitiligo versus 50% or less in generalized vitiligo [25]. A recent review on this argument showed that better surgical results can be obtained in segmental vitiligo and in patients younger than age 20 [26].

Because of the multiple, time-intensive procedures involved in autologous transplantation, these techniques are best suited for repigmentation of limited areas of leukoderma, with priority given to exposed sites. They are reserved for adolescents and adults who are firmly motivated. Surgical therapies are not recommended for patients with a tendency to form keloids or develop hyperpigmentation after minor trauma, and success has not been reported in disorders of hypopigmentation, such as nevus depigmentosus and hypomelanosis of Ito [18].

Techniques of surgical repigmentation involve the transfer of melanocytes, melanocytes and keratinocytes, or full-thickness skin from normally pigmented areas to hypomelanotic patches. Autologous skin grafts can be divided into three major groups: (1) grafting of normal skin (epidermis with or without dermis) that contains melanocytes, (2) grafting of a noncultured epidermal or hair follicle suspension that contains melanocytes, and (3) grafting of cultured melanocytes with or without keratinocytes, in suspension or as sheets [27].

The first group includes different techniques. The thin dermo-epidermal grafts technique involves replacing the achromic lesions of vitiligo

with thin dermal and epidermal sheets that are taken from the donor site with a dermatome at a depth of 0.1 to 0.3 mm to avoid scarring. Superficial dermabrasion is used to prepare the receiving site to the graft. This method is successful in up to 80% of treated patients, avoids scarring, and permits repeated grafts from donor sites [27]. A possible variation is so-called ''seed grafting,'' in which a thin piece of epidermal skin graft is taken from the donor site with a hand dermatome and minced into fragments smaller than 1 mm^2. These pieces are placed on the epidermal-abraded vitiligo lesions and covered with a specific medication for 5 to 7 days. Phototherapy can follow surgery to enhance results [28]. Suction-blister epidermal grafting using suction devices is another similar technique that is popular and yields excellent results [27]. Full-thickness minigrafts (1–2 mm) have become one of the most common surgical methods to treat vitiligo. Multiple donor areas are harvested with a small punch (1–1.2 mm). Minigrafts are placed in the recipient areas, which are prepared depending on the graft type. The grafts range from the removal of ''punches'' similar to those harvested from the donor area to liquid nitrogen–induced blisters, dermabrasion, or laser ablation (eg, Er:YAG laser) and are sealed with sterile adhesive medication. This method allows repigmentation in 1 to 3 months in 70% to 100% of cases by melanocytes spreading from minigrafts [27]. Donor sites are commonly located on the medial upper arms, thighs, or buttocks (''hidden'' sites).

Methodologic variations include flip-top transplants, in which the epidermis at the recipient site is not removed but rather used to form multiple hinged flaps, each covering an ultrathin 1- to 2-mm graft harvested from the donor site using a razor blade [29]. Single-hair grafting techniques from donor sites on the scalp are particularly effective for treating hairy areas, such as the eyelids and eyebrows [30]. Repigmentation of hairs in areas of leukotrichia also has been observed with this and other methods, which suggests a migration of melanocytes from the grafted epidermis to the external root sheath of the hair follicle and then to the hair bulb. Posttransplantation sunlight exposure for 10 to 15 minutes per day or phototherapy can help stimulate melanogenesis [31].

In transplants of noncultured keratinocyte/melanocyte suspensions, donor tissue from a shave biopsy of the buttocks or full-thickness biopsy of the scalp is digested with trypsin and—in the latter case—collagenase to obtain melanocytes from the hair follicles and the epidermis. The cells are put into a suspension for direct application to the recipient site without expansion by culture [32]. This technique is relatively simpler and less time consuming than other methods (especially cell culture methods) and smaller areas can be treated, but rates of success are lower (30%–70%) [33].

Cultural methods can be applied to surgical techniques. Cultured epidermis with melanocytes with or without keratinocytes and cultured melanocytes with or without keratinocyte suspensions can be applied to previously dermabrased recipient areas. The donor sites can be small, and the cells are seeded to stimulate melanocytes and keratinocytes until many more cells—or even a thin epidermal sheet—are obtained and placed on recipient sites previously prepared with one of the various methods. With this technique, satisfactory results are obtained even when treating up to 30% of total body surface, with more than 75% repigmentation rate in more than half of treated patients [27,34]. Small donor areas can be used to cover large hypopigmented areas (up to 500 times larger than the donor site). The achieved repigmentation is relatively uniform, with only minimal textural changes. Cell cultures are more expensive than other surgical methods, require specific laboratory facilities, and require a 2- to 5-week period for the culture, however.

Side effects of vitiligo surgery include Köbner phenomenon of the donor site, keloids, hyperpigmentation, ''cobblestoning,'' scarring, and infection. Careful handling of the donor and recipient sites is mandatory.

Treatment with tissue-engineered skin uses biomaterials such as perforated membranes of semi-synthetic biopolymers of hyaluronic acid 100% esterified with benzyl alcohol. Epidermal culture obtained from normally pigmented sites is optimally delivered to the recipient achromatic patches previously de-epithelized by laser ablation. Excellent and lasting repigmentation without side effects has been reported [27]. Surgical repigmentation techniques can be used with other therapeutic protocols, such as BIOSKIN microphototherapy, to obtain better results [2,5–7,27,34]. Cell culture techniques also can require the use of mitogens to enhance cell growth.

Depigmentation therapy

In patients with extensive areas of depigmentation or disfiguring lesions that do not respond to repigmentation therapies, therapeutic

depigmentation of the residual pigmented areas of the skin should be considered. Patients should be informed that therapeutically induced depigmentation is permanent and irreversible and that they always will be at risk of suffering sunburns, premature ageing, and cutaneous neoplasms. It is necessary to minimize sun exposure and apply broad-spectrum sunscreens.

The US Food and Drug Administration approved the use of monobenzyl-ether of hydroquinone (MBEH) for depigmentation in patients who have vitiligo that involves more than 50% of their body surface area. People who suffer from a less widespread vitiligo can benefit from depigmentation therapy, however, particularly because alternative modalities have been developed. Recently, the sequential use of 4-methoxyphenol and the Q-switched ruby laser [35] and cryotherapy [36] have been reported as alternative options for depigmentation therapy, with promising results.

4-Methoxyphenol (p-hydroxyanisole, MBEH, or mequinol) is a phenol derivative with melanocytotoxic properties (similar to those of MBEH) that has been used in patients who have vitiligo with results comparable to those obtained by MBEH [35]. It is considered a good alternative to MBEH because in many European countries the latter is no longer available, mainly because of its side effects. As for MBEH, the indication for using 4-methoxyphenol includes only depigmentation in patients who have vitiligo.

A recently developed depigmentation therapy for vitiligo is based on the use of Q-switched ruby laser, which has a wavelength of 694 nm and is capable of selectively destroying melanin and melanin-containing structures of the skin [37]. The risk of scarring is minimal, and depigmentation is rapidly achieved (7–14 days) compared with bleaching agents (1 month–1 year). Pain caused by the procedure can be managed easily by applying a topical anesthetic cream before the procedure. Because laser treatment is thought to induce depigmentation as a result of koebnerization, patients with a negative Koebner phenomenon should not respond to treatment. These data were confirmed by observations by Njoo and colleagues [35] that after a treatment-free period of 2 to 18 months, a perifollicular pattern of repigmentation can appear in patients with negative Koebner phenomenon but not in persons with positive Koebner phenomenon, which seems to be a favorable prognostic sign for the long-term results of Q-switched ruby laser depigmentation. Q-switched ruby laser, like chemical depigmentation, does not seem to kill follicular melanocytes.

Cryotherapy has been used recently for depigmentation in patients who have vitiligo because of its known melanotoxic capabilities [36]. In this study, five patients were treated with one to three sessions of cryotherapy, and all of them achieved complete depigmentation with no side effects. After 8 months follow-up, two patients showed partial lentigo-like repigmentation on sun-exposed areas, which was retreated with cryotherapy or chemical peeling. Repigmentation is still a problem, however, as is the case with all depigmentation methods known thus far [38].

Alternative treatments for vitiligo

Alternative treatments include light exposure plus L-phenylalanine (oral or topical), khellin (topical), melagenina I and II (topical), and topical minoxidil treatment. Homeopathy, ayurvedic medicine, and climatologic and balneologic therapies also have been proposed [39].

Summary

Vitiligo and other hypomelanoses can be treated successfully with medical, physical, and surgical techniques with excellent results. Therapeutic strategies are being developed to minimize the side effects of previous treatments and are used for children with vitiligo. To reach optimal clinical results in terms of repigmentation and minimizing side effects, narrow band UVB–focused treatment represents the treatment of choice when vitiligo affects less than 10% of the skin surface [40].

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