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Depigmentation Therapies in Vitiligo

Sanjeev Mulekar, Madhulika Mhatre and Swapnil Mulekar

Abstract

Vitiligo is a chronic condition characterized by white patches on normal-appearing skin. It runs an unpredictable course. Main reason of stress in vitiligo patients is the presence of two colors on the skin surface. The aim of the treatment is to achieve normal skin color. Depigmentation is considered when repigmentation is not possible or the patient is willing to accept that repigmentation is not possible and opt for irreversible depigmentation. The only agent approved for depigmentation is monobenzyl ether of hydroquinone or monobenzene for patients with more than 50% of body surface area affected with vitiligo. The scope of this chapter is to describe modality of depigmentation and its risks and benefits.

Keywords: extensive vitiligo, vitiligo, depigmentation, MBEH

1. Introduction

Vitiligo is a skin condition characterized by loss of pigments on normal skin with a worldwide prevalence of 0.1–2%. Due to its cosmetic impact, vitiligo can impact the quality of life in children and adults. There are multiple therapies used for repigmentation beginning from topical corticosteroids, calcineurin inhibitors, and narrowband ultraviolet B (NB-UVB) to oral systemic medications and surgery. Even though a good number of patients may achieve successful repigmentation, there may be a few in whom the progression of vitiligo may affect extensive body surface areas making repigmentation an uphill task. The aim in such patients with extensive vitiligo (more than 50% body surface area) would be to achieve a uniform skin tone by depigmenting the remaining pigmented sites [1].

Depigmentation therapy is an accomplishable alternative therapy in patients who are extensively affected by vitiligo. It can be used in all skin types. Most readily used and available depigmenting agents are monobenzyl ether of hydroquinone (MBEH), 4-methoxyphenol, and phenol. Other therapies such as lasers and cryotherapy have also been used. The depigmentation process is a gradual one and can take anywhere between 1 and 3 years. In the author's experience, those who have undergone depigmentation are satisfied and happy with the therapeutic outcome if one achieves uniform color.

1.1 What the research says

The depigmentation approach is quite recent and is derived from the observations of unwanted depigmenting action of the phenol derivatives [2]. However, there are very few published studies on it. The aim of the researchers

was to explain the possible mechanism of action for this class of compounds. Tyrosinase was the first suggested target. Also the potential of different phenol derivatives to act as an alternative substrate of the enzyme or as a competitive inhibitor was evaluated. Thus, it was hypothesized that this class of substances, or some of them, may be used for the treatment of skin disorders caused due to hyperpigmentation or melanocyte hyperproliferation. Further structural studies have indicated that the role of the position and type of substitutes in the phenolic ring allow the compound to be hydroxylated or oxidated by tyrosinase [3]. Considering phenol derivatives have a role in this process, hydroquinone was evaluated. Hydroquinone (HQ) belongs to the phenol/catechol class of chemical agents. Tyrosinase gets inhibited by HQ when interaction occurs with copper at the active site. This further decreases the amount of intracellular glutathione and induces the production of oxygen-reactive species. Thus, HQ acts as an alternative substrate, according to most part of phenol/catechol compounds, because it is similar to tyrosine. The enzyme can thus oxidize HQ without generating the pigment. The quinones produced are able to react with the sulfhydryl residues of the proteins, generating oxidative damage and affecting the cell growth. The depigmenting action is the result of the oxidative damage, involving both lipids and proteins of the cellular membranes. Functional studies have demonstrated that HQ and other phenolic compounds, such as tert-butylphenol, may even act through different mechanisms, including the oxidation of TRP1, and by interfering with RNA and DNA synthesis. HQ has been identified as the main depigmenting agent, whereas among the various phenolic derivatives, the monobenzyl ether of hydroquinone (MBEH) appeared as the more handful one. In this chapter, we will review and compare various established and potential depigmentation agents as well as emerging therapies that can be used in extensive and universal vitiligo.

2. Selecting the right candidate

Selection of an appropriate patient is of utmost importance in depigmentation therapy. The option of depigmentation should be made available to only those patients having extensive vitiligo. Detailed and thorough consultation sessions should be conducted with the patient and their families (preferably 2–3 sessions), explaining to them in detail that this therapeutic modality utilizes a potent depigmenting agent and should not be used for cosmetic purposes [2, 3]. They should be explained with all realistic expectations, treatment time frame, the cost involved, and side effects if any, and that once one particular type of treatment is done, they will not be a good candidate for any other type of treatment. Subjects with skin types (V and VI) with a disfiguring contrast between dark-pigmented skin and white vitiliginous areas, especially involving exposed areas (face or the hands), may be a candidate for depigmentation. Moreover, incomplete or trichrome repigmentation (e.g., when using UV light) may cause more disfigurement, thus making such individuals good candidates for depigmentation therapy. The patients should be informed that even after depigmentation, spontaneous repigmentation might occur in vitiligo lesions, warranting additional depigmenting cycles. Patients must be informed that these treatments lead to a definitive irreversible depigmentation. Younger patients with extensive involvement can be given an option of repigmentation instead of opting for depigmentation explaining that complete repigmentation may or may not be achieved. Depigmentation therapy should be avoided in children less than 12 years of age [4].

3. Topical therapies for depigmentation

3.1 Monobenzyl ether of hydroquinone (MBEH)

MBEH (monobenzene, p-benzyloxy-phenol) is the most common topical depigmenting agent used mainly because it is the only product approved by the United States Food and Drug Administration (USFDA) for depigmentation in vitiligo, if the affected body surface area is more than 50% [1]. It is a hydroquinone (HQ) derivative and was first introduced in 1930s. MBEH is the first-line agent for depigmentation therapy in vitiligo patients.

3.1.1 Mechanism of action

There are multiple pathways through which MBEH causes depigmentation [5]:

1. Reaction with tyrosinase enzyme during melanin synthesis leads to conversion of MBEH to quinones. The reactive quinone products formed bind with cysteine found in tyrosinase proteins (sulfhydryl (-SH) group) to form hapten-carrier compounds resulting in formation of neoantigens. These neoantigens stimulate a systemic, melanocyte destruction and an inflammatory reaction.
2. Another result of MBEH conversion by tyrosinase is production of reactive oxygen species (ROS). ROS leads to lysosomal degradation of melanosomes. Additionally, there is interference of the melanosome structure and membranes, following which the major histocompatibility complex (MHC) class I and II routes and initiation of melanocyte Ag-specific T-cell responses cause an increase in surface expression of melanosomal antigens.
3. ROS also contributes to an innate immune response due to the release of exosomes.
4. MBEH-exposed skin presents with rapid and persistent innate immune activation. It is quoted by Gupta et al. "that MBEH is a contact-sensitizer, inducer of a type IV delayed type hypersensitivity response against the quinone hapten. However, this only occurs if there is production of pro-inflammatory cytokines such as interleukin (IL)-1b and IL-18 by the Langerhans cells or keratinocytes" [6].

There have been reports that when MBEH therapy was combined with all-trans retinoic acid (ATRA), it enhanced depigmentation process and the melanocytotoxic effects via inhibition of the enzyme glutathione S-transferase in melanocytes. This could be a possible way to avoid contact dermatitis when using high concentrations of 40% MBEH. However, combination of ATRA-MBEH did not affect hair pigmentation in animal studies [7].

3.1.2 Administration of treatment

After the patient has been duly consulted and informed about all the possible outcomes and consequences of the treatment, the depigmentation therapy is initiated. Application of MBEH can be done by the patient at home. Initially, the exposed areas are treated. A test spot is advised over a normal pigmented skin (usually forearm) to assess the development of contact dermatitis. If there is no

adverse reaction, the patient can continue with the application of the cream on the areas of top priority and then move in stages for low priority areas. To avoid contact dermatitis, different concentrations of MBEH can be used. MBEH can be diluted to 5% for use on the neck, 10% on the face, and 20% on the arms and legs. In patients who fail to respond to 20% MBEH over a course of 3 to 4 months, the concentration of MBEH can be increased to 30% and then further to 40%. Concentrations of 30 and 40% MBEH have been used primarily on the extremities, especially the elbows and knees. Concentrations greater than this are not recommended [8].

It takes anywhere between 4 and 12 months for gradual depigmentation [8]. It is to be noted that depigmentation is mostly irreversible and histologically associated with loss of melanosomes and melanocytes [1].

3.1.3 Precautions

Patients should always be informed and well instructed about certain precautions while using MBEH.

1. Application of MBEH at one site can lead to loss of pigment at distant body sites, i.e., application of MBEH to the arm may result in loss of pigment on the face [4]. Moreover, it can also reactivate a stable disease.
2. Application of MBEH to the eyelids is not advised [8] because of risk of ochronosis. It may lead to pigmentation of the conjunctiva if MBEH is applied on the eyelids.
3. Avoid skin-to-skin contact on a continuous basis with another person as it can cause a decrease in pigmentation at the site of contact in the other person.
4. The use of sunscreens with a high-sun protection factor (SPF) is essential. This also helps to prevent repigmentation as well as sunburn reactions [4].
5. Follicular repigmentation may occur spontaneously upon sun exposure [8]. This happens mainly because MBEH only destroys epidermal melanocytes keeping follicular melanocytes intact.

3.1.4 Side effects

Irritant contact dermatitis and common allergic reactions can develop [9]. In which event, application of MBEH is stopped, and open wet dressings are applied to the affected area along with topical steroids. Once the dermatitis has subsided, MBEH can be restarted at a lower concentration of 5% [8]. Other side effects include exogenous ochronosis [10], unmasking of telangiectasias and phlebectasias on the lower extremities [8], pruritus, xerosis, erythema, rash, edema, conjunctival melanosis, and distant depigmentation [4].

Risk of carcinogenesis with MBEH has not been reported but cannot be ruled out, and hence it is banned from the European Union since 2001 in cosmetics [11].

3.1.5 Combination therapy

All-trans retinoic acid (RA), which is a vitamin A derivative primarily employed in the treatment of acne, is shown to serve as a weak depigmenting agent when used for several weeks.

A combination of RA and MBEH induced significant depigmentation within 4–8 weeks. Nair et al. proposed that RA might enhance the skin penetration of depigmenting agents. Thus, RA increases the susceptibility of melanocytes to hydroquinone and 4-hydroxyanisole via the impairment of glutathione-dependent defense mechanisms of melanocytes and reducing melanogenesis activity in viable melanocytes [12–15].

3.2 Monomethyl ether of hydroquinone/4–0 methoxyphenol

This compound is a phenol derivative and is also known as p-hydroxyanisole (HA) or mequinol [1].

3.2.1 Mechanism of action

Mequinol acts in the similar way as MBEH acts. This compound usually acts via a dose-dependent response manner. It can be used as monotherapy or in conjunction with a Q-switched ruby laser.

3.2.2 Administration of treatment

The compound is used in a 20% concentration in an oil/water cream base. As with MBEH, cream is applied on an initial test patch to observe for any allergic reactions. If there are no reactions, the patient is advised to apply cream twice daily until complete depigmentation is observed [16]. The effectiveness of 4-MP has been correlated with the duration of the use of the cream; the longer the cream was used, better the results that were obtained [1].

A combination product of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin was tested in a double-blind multicentric study and was found to significantly improve solar lentigines and related hyperpigmented lesions of the face and hands after a twice-daily application of up to 24 weeks [1].

3.2.3 Side effects

Side effects include mild burning or itching, irregular leukoderma, contact dermatitis, ochronosis, and risk of carcinogenesis cannot be ruled out [11]. Protection from sunlight is necessary or repigmentation risk is high [1, 11].

3.3 Phenol solution (88%)

Phenol is an inexpensive peeling agent having medium-depth capability and used for treatment of photodamage or rhytids. The toxicity of phenol toward melanocytes is well documented. Phenol has the ability to penetrate deeper into the tissue up to the upper reticular dermis.

3.3.1 Mechanism of action

Phenol is involved in melanogenesis, inducing coagulation of protein in the epidermis. The melanocytes lose their capacity to synthesize melanocytes normally. This property of phenol is different than that of MBEH and hydroquinone wherein they destroy the melanocytes [17]. Hence, 88% phenol can be used as therapeutic option to eliminate residual normally pigmented lesions in patients.

3.3.2 Administration of treatment

The area to be treated is cleaned with spirit/alcohol. Application of phenol is done with the help of a swab soaked with phenol until cutaneous frosting occurs. There might be a burning sensation experienced by the patient for approximately 60 seconds, which gradually decreases in intensity but can last from minutes to hours. In a case study reported by Zanini and Machado Filho, they reported the use of 88% phenol on a 62-year-old female patient. Post 2 sessions, with a gap of 45 days, total elimination of residual pigmentation was achieved [17].

3.3.3 Side effects

In general, 88% phenol does not produce any major complications when used in limited areas. However, some complications such as cardiotoxicity and other systemic toxicities have been reported in patients treated with medium and deep peeling over larger areas. Its cellular uptake is both rapid and passive because of its lipophilic character and signs of systemic toxicity develop soon after exposure. Cardiovascular shock, cardiac arrhythmias, and bradycardia, as well as metabolic acidosis, have been reported within 6 hours of skin-peeling procedures with phenol [17]. Other complications include non-esthetic scar formation, dyschromia, and development of herpetic eczema. However, the authors of this chapter have also noted a paradoxical response, wherein phenol application led to repigmentation of the skin!

4. Physical therapies for depigmentation

Depigmentation with topicals is effective; however, they come with their share of side effects and can take up to 10 months or more for completion of the process and rarely complete depigmentation may not be achieved. Depigmentation by physical means, i.e., by cryotherapy and lasers, can be done when rapid depigmentation is desired or when patients have not responded well to topicals or have had contact dermatitis or any side effects due to the same.

4.1 Cryotherapy

Cryotherapy is nothing but cold therapy or the use of low temperatures to treat a variety of tissue lesions. With cryotherapy, it is possible to achieve rapid and permanent depigmentation via irreversible tissue damage resulting from intracellular ice formation. Liquid nitrogen is used as a cryogen for clinical use. The degree of damage depends on the rate of cooling and minimum temperature achieved. Further, inflammation develops within 24 hours of the treatment, which contributes to destruction of lesions via immunologically mediated mechanisms. In areas of koebnerization, cryotherapy is more effective.

4.1.1 Procedure

Initially, spot testing by a single freeze-thaw cycle is done. Once the edema and erythema subside, patches are treated with cryotherapy 3–6 weeks later. Either CO₂ or liquid N₂ can be used. A 2-cm flat-topped and round cryoprobe is used at approximately 40 mm from the skin surface. The whole patch is frozen with a single freeze-thaw cycle from the periphery followed by forming successive rows inward.

Procedure should be terminated when a narrow (<1 mm) frost rim forms around the periphery of the cryoprobe. The rim can develop within 10–20 s by a cryogun connected to a container with barometric pressure above 80 kg/cm². For lesions around the orbits or uneven areas of the nose, cryoprobes having smaller diameters may be required. No more than one freeze-thaw cycle is advised per session. There have been cases reported which have used two freeze-thaw cycles [18]. Results are visible by the end of 4 weeks after the procedure.

Alternatively, a cryospray/cryopen or the traditional dip-stick method of application can be used following the same freeze-thaw cycle protocol.

4.1.2 Pros and cons

- Low cost and simple to perform.
- Does not require anesthesia.
- Minimal wound care with no dressing or antibiotics.
- Safe and efficacious.
- No scar formation if performed by an experienced dermatologist.
- It can be performed only on smaller areas.
- Multiple sittings may be required.
- If performed aggressively, it can lead to permanent scarring.

4.2 Laser therapy

Another faster method of depigmentation is the use of laser therapy. Lasers have been advocated more than MBEH and other bleaching agents due to their failure rate, as they have been proven to selectively destruct the melanocytes causing depigmentation. Further the risk of scar formation is minimized with laser therapies [16].

Mainly, the Q-switched ruby (QSR, 694 nm) and alexandrite (755 nm) lasers have been used in depigmentation. Both of these lasers operate in a similar manner in terms of mechanism of action. They induce photothermolysis of the pigmented lesions as they have wavelengths between 600 and 800 nm. These wavelengths are more readily and well absorbed by melanin. The frequency and pulse width is adjusted according to the skin type of the patient by a trained and experienced dermatologist. A maximum of 80 cm² area is treated per session.

| Q-switched ruby | Q-switched alexandrite |
|--|--|
| <ul style="list-style-type: none">• Selectively targets melanosomes and destroys melanocytes and keratinocytes• Works better on tanned skin• Fast and safe• Duration of treatment is short• Larger areas can be treated effectively• Reduced risk of scar formation | <ul style="list-style-type: none">• Is efficacious in treating naturally occurring pigmented lesions as well as exogenous pigments• Safe, simple, and effective in treating recalcitrant pigmentation• Faster pulse frequency, hence rapid therapy• Higher wavelength so greater tissue penetration with improved results |

Some other potential Q-switched lasers that can selectively destruct melanocytes include neodymium:yttrium aluminum garnet (Nd:YAG) laser (1064 nm) and the frequency-doubled Q-switched Nd:YAG laser (532 nm) [1]. In a study by Boen et al., Q-switched ruby laser (QSRL) 694 nm, Q-switched alexandrite laser (QSAL) 755 nm, and picosecond 755-nm alexandrite lasers provided the most significant pigment reduction when different recalcitrant pigmented areas of the body were treated by the abovementioned lasers over different areas in the same patient. In all the patients treated with this laser therapy, no adverse reactions apart from mild postprocedure erythema and crusting were noticed. The picosecond laser poses more advantages over the traditional Q-switch laser as it has increased photochemical action due to shorter pulse duration, requires lesser treatment sessions, and has reduced specific photothermal damage. This results in an increase in the safety profile of the laser and improves the effectiveness of this therapeutic modality [19, 24–26].

4.2.1 Points to ponder

- Procedure is slightly painful and may require local anesthesia.
- Treatment is expensive.
- Possibility of failure in removing pigmented patches even after several treatments because of Koebner's phenomenon.
- Patients with active vitiligo respond better to laser treatments compared to those with stable vitiligo. Hence, patients who are Koebner negative may often relapse [16].

5. Emerging therapies for depigmentation

5.1 Imatinib

Also known as imatinib mesylate, it is used to treat conditions like leukemia and gastrointestinal stromal tumors. It was observed that patients treated with imatinib were reported to develop generalized depigmentation as a side effect. Imatinib is a tyrosinase kinase inhibitor, thus inhibiting the activity of the enzyme, resulting in decreased pigmentation of the skin. The side effects of imatinib include fluid retention, periorbital edema, diarrhea, and myelosuppression. Some of the dermatological side effects include erythroderma, follicular mucinosis, and lichenoid eruption [27].

5.2 Imiquimod

Imiquimod is usually used for topical treatment of anogenital warts and basal cell carcinomas [20]. It is an imidazoquinoline and is an immune response modifier. It acts by stimulating the monocytes/macrophages and plasmacytoid dendritic cells in dermis and epidermis of the immune system to produce pro-inflammatory cytokines, mainly interferon α and other signals that activate T-cell-mediated response leading to apoptosis of tumor cells. Prolonged use of imiquimod has shown to result in depigmentation [1]. Imiquimod also stimulates CD8 cells to become cytotoxic and enhances antigen presentation [21]. Recently, it was reported that human melanocytes express toll-like receptor 7 (TLR7). When applied topically, imiquimod binds to TLR7 followed by stimulation of various cytokines, which induce the abovementioned T-lymphocytic response [22]. Imiquimod also has a direct action on melanocytes via

apoptosis of melanocytes. This action is related to reduction of expression of Bcl-2 and/or an increase in the proapoptotic stimulus (cytotoxic T lymphocytes, natural cytotoxic T cells/killer cells, granzymes B, Fas, TNF, Bax, etc.) [23].

Thus, there is a strong possibility that imiquimod may cause elimination of melanocytes by direct influence on cells as well as inducing acquired immunity indirectly, which eventually induces vitiligo-like hypopigmented lesions [28]. Some common side effects include itching, pain, burning, erosions, erythema, and crusting.

5.3 Diphenacyprone (DPCP)

DPCP is used traditionally as a treatment modality for alopecia areata. Depigmentation was found to be one of the side effects due to the use of DPCP. It has an immunomodulatory mechanism of action. As reported by Duhra and Foulds [12], in a case of alopecia totalis where topical DPCP was used, there was a marked reaction with erythema and edema on the forearm after 3 days, but the scalp manifested only slight macular erythema. The reaction on the forearm subsided after 2 weeks and was replaced by a depigmented patch over a period of 6 weeks. Upon incubating the affected skin with dopa followed by electron microscopy, an absence of melanosomes and melanocytes was revealed. It has been observed that vitiligo can develop even with DPCP concentrations as low as 0.0001% [12].

Some of the adverse effects include hyperpigmentation, regional lymphadenopathy, blistering, and eczematous reactions [20].

6. Limitations

The science of depigmentation is still not a perfected one and that does leave many questions unanswered. Further research in this arena can help shed light on these doubts:

1. Aspects that cannot be controlled
 - a. Remote depigmentation.
 - b. End result (color matching or same color).
 - c. Hairs do not lose pigment (can give repigmentation especially follicular).
 - d. Repigmentation during pregnancy (at times extensive).
 - e. Resistance to MBEH.
2. Can patients with less than 50% involvement, willing to accept that no more repigmentation is possible, are candidates for depigmentation?
3. Whether depigmentation in children is a safe and viable alternative?

7. Conclusion

Vitiligo has a huge psychological impact and is also socially stigmatizing, particularly for patients with darker skin types in whom the contrast between the

vitiliginous lesions and uninvolved skin can be especially apparent and disfiguring. In patients with widespread involvement covering more than 50% of their body and in cases where medical modalities including phototherapy have proved ineffective, depigmentation therapy should be considered. Patient selection, adequate counseling, and patient education are extremely important for a positive long-term outcome.

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