Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: http://www.tandfonline.com/loi/ieop20

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To cite this article: Xingang Wang PhD, John McCoy PhD, Torello Lotti MD & Andy Goren MD (2014) Topical cream delivers NB-UVB from sunlight for the treatment of vitiligo, Expert Opinion on Pharmacotherapy, 15:18, 2623-2627

To link to this article: http://dx.doi.org/10.1517/14656566.2014.978287

Published online: 03 Nov 2014.

EXPERT OPINION

Topical cream delivers NB-UVB from sunlight for the treatment of vitiligo

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Ultraviolet-B (UVB) phototherapy for the treatment of vitiligo is an effective first-line choice. However, the cost of multiple doctor visits and the lengthy treatment regimen has resulted in low compliance, limiting access to this safe and effective mode of treatment. Topical Photocil represents an innovative solution to this problem. The drug selectively filters solar radiation to deliver narrow-band UVB to vitiligo lesions. Here, we discuss how this novel topical cream could provide a convenient alternative to artificial light phototherapy.

Keywords: Photocil, phototherapy, topical, vitiligo

Expert Opin. Pharmacother. (2014) ***15****(18):2623-2627*

1. Introduction

Vitiligo is a common depigmenting skin disorder characterized by the appearance of white macules on the skin, mucosal and hair. It affects about 0.1 – 2.0% of the world population, irrespective of sex, race and age [1]. The exact pathogenesis of vitiligo remains elusive, but many possible factors may contribute to its development. Autoimmune, genetic, biochemical, viral and oxidative state anomalies have all been suggested to have influence on the development of vitiligo [1,2]. Currently, there is no cure for vitiligo.

2. Current treatment options

There are several types of treatments available for vitiligo, including topical treatments, phototherapy, systemic drugs and surgery [3,4]. None of these treatments is 100% effective and some are associated with relevant side effects. Accordingly, there is still great demand for the development of novel and effective therapies.

2.1 Topical treatments

Topical treatments with corticosteroids, vitamin D analogs or calcineurin inhibitors have been commonly used as first-line therapies for vitiligo. Corticosteroids act by modulating immune response, as well as inducing melanocyte activation. They demonstrate best results (up to 75 % repigmentation) on sun-exposed areas [4]. Corticosteroids may produce side effects, such as skin atrophy, telangiectasias, folliculitis, acneic lesion and hypertrichosis. As such, they are applied sparingly to small areas and can only be used for a limited duration. Calcineurin inhibitors block the activity of calcineurin, which activates the expression of many cytokines involved in vitiligo such as TNF-α and IFN-γ [5,6]. Calcineurin inhibitors have been shown to be as effective as corticosteroids; however, their use has been restricted in the US due to incidence of cutaneous and noncutaneous lymphomas [7]. Vitamin D analogs seem to activate melanogenesis in cooperation with UV exposure only.

10.1517/14656566.2014.978287 © 2014 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

2.2 Surgery

Surgery for vitiligo involves grafting pigmented skin or melanocytes onto the surface of achromic skin. Donor sites are chosen from unaffected areas of skin on the vitiligo patient. The successful repigmentation rate of skin grafting is usually > 50% of graft area in > 50% of cases in adults [8]. The risk of adverse events includes scar formation at the donor site, cobble stoning of the acceptor area and recurrence of depigmentation. Surgery for vitiligo is normally a third-line treatment, used when other treatments (topical treatments and phototherapy) fail.

Melanocyte transplantation is a more complicated procedure involving the isolation of melanocytes from a donor site. The benefit of this method is that cells from one small area of donor skin are sufficient to cover 10 times the area of depigmented skin [9]. With further culture of harvested melanocytes, coverage can be extended. Successful repigmentation (over 70%) has been reported in 62% of vitiligo lesions transplanted with noncultured melanocytes compared with 52% of vitiligo lesions treated with cultured melanocytes [10].

2.3 Phototherapy

Phototherapy with either excimer laser or lamp is a safe and effective treatment for vitiligo. The monochromatic light (308 nm) of the eximer laser penetrates deeper into the skin compared to narrowband ultraviolet-B (UVB) (NB-UVB) or ultraviolet-A (UVA) [11]. However, repigmentation rates are similar between the different options; patients commonly achieving 75% of repigmentation after a 36 weeks of treatment [12].

NB-UVB phototherapy is considered to be the gold standard of treatment for patients with generalized vitiligo. It has gained prevalence over psoralen plus UVA (PUVA) because it has similar efficacy and fewer side effects [13,14]. Clinical trials have reported > 75% repigmentation was achieved in 12.5 – 75% of treated patients after ~ 1 year of treatment [15]. Some factors affecting the percentage of repigmentation are age (younger patients respond better), duration of disease (recent vitiligo onset responding best) and the location of vitiligo lesions (acrofacial vitiligo demonstrating the best response to NB-UVB) [16,17].

The exact mechanism of phototherapy is still poorly understood, however, it has been suggested that UVB induces melanogenesis and migration of melanocytes mediated by several factors such as IL-1, TNF-α and leukotriene C4 [18,19]. Phototherapy is also found to reduce oxidative stress, which has been proposed to be an important factor causing melanocyte destruction [20]. After UVB phototherapy, the erythrocyte oxidant marker melonyldialdehyde level is significantly reduced, while the antioxidant marker glutathione peroxidase is significantly increased [2]. This would suggest that combining antioxidant agents with NB-UVB may improve efficacy. Other therapies like topical calcineurin inhibitors and vitamin D analogs have also been reported to improve NB-UVB treatment [21].

Compliance is a major drawback in the effective application of phototherapy [22,23], because of the lengthy treatment regimen. The equipment required to administer the treatment is costly and the safety requirements for applying high doses of radiation require a physician's guidance. As such, the majority of treatments are performed at a physician's office or a clinic. Typical treatment regimens require 2 – 3 visits per week for as long as 1 year to achieve appreciable benefit. The time commitment and cost of visits are often not realistic for many patients and compliance rates are low despite the high efficacy of the treatment [22,23].

3. Alternative phototherapy

3.1 Photocil provides a convenient alternative to artificial light-based phototherapy

The sun emits an abundance of accessible UV radiation, including NB-UVB, which could be exploited for the treatment of vitiligo. Solar radiation could provide a suitable substitute for traditional UVB phototherapy conducted at clinics. Unfortunately, not all of the radiation content produced by the sun is therapeutic for vitiligo. In order to use endogenous solar UVB, an appropriate filter must be applied to bias solar radiation away from nontherapeutic wavelengths of UV light (most notably, wavelengths below 300 nm). Attenuating radiation at the lower end of solar UVB is critical for delivering phototherapy from the sun. This is supported by examples from nature; attenuation of lower UVB (< 300 nm) is reported to occur naturally at the Dead Sea in Israel [24]. At the Dead Sea, the extra depth of the atmosphere (400 m) filters solar radiation and attenuates the lower range of the UVB spectrum. Many examples of heliotherapy conducted at the Dead Sea have been reported as therapeutic for dermatological conditions, including psoriasis, vitiligo and atopic dermatitis; many studies have reported improvements on par with artificial light phototherapy [25-27].

Inspired by this phenomenon, McCoy *et al.* [28] describes the development a topical drug used to filter nontherapeutic radiation from solar UV. The drug biases radiation from the sun toward a therapeutic wavelength of 311 nm, allowing radiation in the NB-UVB range to pass through for treatment. The drug offers a convenient alternative to the multiple trips to the clinic needed for artificial light phototherapy. In addition, the drug makes phototherapy an available treatment option for less severe cases of vitiligo, where traditional phototherapy would not be economical.

3.2 Clinical evaluation of Photocil for vitiligo

To investigate the clinical effectiveness of Photocil phototherapy, Goren *et al.* [29] performed a double-blind placebo-controlled study, in which 15 patients were exposed to sunlight after applying Photocil cream or a placebo having the same sun protection factor to vitiligo-affected areas. The study addressed acrofacial vitiligo only, as these lesions were the most amenable to sun exposure in the public setting

outside the clinic. All lesions studied were diagnosed as stable. Only end point data was reported, and thus no time-dependent repigmentation data was provided.

Following an average of 11 weeks of treatment (three sessions per week), all the patients in the drug arm responded favorably to therapy. Specifically, 28% of patients had 70% or more surface area repigmentation, 28% had at least 50% repigmentation, and 44% had 30 – 40% repigmentation. In sharp contrast, only 10% of the placebo control group had at least 20% repigmentation.

The pilot study suggests Photocil cream outperforms heliotherapy at the Dead Sea, and is comparable to NB-UVB artificial light therapy [30]. No adverse events were reported in the study excluding slight erythema during minimum erythemal dose (MED) determination. Additional pilot studies have been conducted in patients with psoriasis [31], however, the details of these studies are beyond the scope of this communication. Briefly, positive results were also demonstrated in the psoriasis, suggesting Photocil phototherapy is applicable in most cases where traditional NB-UVB phototherapy is used.

3.3 Dosage and %MED calculations for phototherapy with Photocil

In clinical application of artificial light phototherapy (NB-UVB), dosage can be calculated directly from the known irradiance of the light booth. Because the intensity of radiation from the light booth is constant, tailoring ideal dosages for each patient is straightforward and amounts to an exposure time (e.g., 60 s) spent in the booth. The amount of radiation required to produce erythema or the MED can be found empirically by exposing small areas of skin to increasing exposure times and observing the amount of time required to produce erythema. In comparison, solar irradiance is not constant and changes depending on many factors, including time of day, global position and weather. As such, calculating dosages of phototherapy with Photocil presents new challenges, fortunately, ones that can be overcome.

During the clinical trial described previously, direct measurements of solar UV (measured with a UV radiometer) were taken before each patient's phototherapy session. Based on the amount of available solar radiation, treatment times could be calculated using the patient's skin type and a standardized MED chart [29]. Unlike the clinical trial, at-home use of Photocil will not have the benefit of direct UV measurement for the calculation of treatment times. An alternative to directly measuring UV is to use a computer weather models to estimate solar UV based on current weather, time of day and global position. Such models are available, and have been implemented for use with Photocil. The models give excellent approximations of solar UV content and may even provide more accurate dosage than the measured UV data used with a chart. Current clinical trials are underway to evaluate Photocil phototherapy using dosages calculated with weather models. Patient's temporal and position data is either entered manually (by the patient) via a phone-based system or sent directly via global positioning systems from a mobile device (i.e., the calculation interfaces with a mobile application). The aim of these systems is to provide patients with the ability to conduct successful solar-based phototherapy at home with minimal interaction with their physician.

3.4 Limitations of sunlight phototherapy with Photocil

Phototherapy with Photocil offers a convenient alternative to the photo booth for patients with vitiligo. However, the requirement of available UV restricts its use to certain months of the year, depending on the patient's location. Photocil use would typically be restricted to late spring and summer months; however, at certain locations sufficient UV will be available for more months of the year. The same limitation applies to patients who cannot schedule therapy sessions near midday, as the intensity of UV radiation is greatest at solar noon. Therapy sessions conducted at times long before or after solar noon may require too much exposure time to be practical for patients. In addition, the outdoor treatment option may not be suitable for vitiligo lesions occurring on regions of the body that cannot be exposed in public. For example, Photocil would not be appropriate for genital vitiligo.

4. Conclusion

Phototherapy using topical Photocil has been shown to compare favorably to previously reported results using NB-UVB and heliotherapy conducted at the Dead Sea for the treatment of vitiligo [29]. Given the at-home feature of this drug, Photocil could provide a convenient alternative to artificial light phototherapy. The abundance of the sun combined with the lower cost of the treatment could increase patient compliance and satisfaction with phototherapy. Additionally, Photocil could provide a phototherapy option for many patients who currently do not have access. For example, it can be used for patients with mild vitiligo, where traditional phototherapy is not economical or practical.

Large-scale clinical trials are still needed to assess the general efficacy and any possible side effect of Photocil cream in different races, ages and so on. Additionally, combination therapies including Photocil used with other treatments (e.g., surgical or other topicals) should be explored. For instance, it has been shown that the combination of NB-UVB and tacrolimus ointment (0.1%) is more effective than UVB treatment alone in vitiligo patients [32]. Combination studies with Photocil may have similar benefits. Nevertheless, Photocil offers a solution to the compliance issues of phototherapy and is a welcome addition to novel innovative treatments for vitiligo.

5. Expert opinion

Vitiligo is a complex disorder in which the presentation of white depigmented patches on the skin and/or on the mucosal body surface is frequently the most common visible epiphenomenon of underlying systemic alterations. In the vast majority of cases (namely in the nonsegmental forms of vitiligo, with exceptions), the disease is, in fact, a truly systemic disease in which the involvement of the melanocytes beyond the skin can produce more or less clinically relevant signs and symptoms. Melanocytes and melanoblasts are located in the human body not only in the epidermis but also in the hair, eye (in both the retina and in the uvea), inner ear, brain, heart and fat tissue [33,34]. However, the physiological, pathophysiological and clinical implications of the involvement of the melanocytes located beyond the skin in the different clinical forms of vitiligo are outside the scope of this communication. Here, we focus on the description of a novel topical therapeutic approach, Photocil, recommended for all clinical forms of vitiligo.

The rational clinical approach to each vitiligo patient is based on some essential steps including: i) diagnosis of the specific clinical form of vitiligo and evaluation of possible and clinically relevant involvement of the melanocytes located outside the skin [34]; ii) treatment of the different systemic conditions depending on the involvement of the melanocytes located outside the skin [33,34]; iii) global evaluation and treatment of the overall psycho-neuro-endocrine-immune dysregulation of the individual vitiligo subject [35]; iv) diagnosis and treatment of commonly associated cutaneous and systemic disorders [33-35]; and v) systemic treatments oriented both to expedite the cutaneous and mucosal repigmentation and to prevent further spreading of the 'vitiligo disease,' including the well-established and/or the recently introduced systemic corticosteroids, minocycline, antioxidants, immunomodulators and the promising administration of oral low-dose basic fibroblast growth factor [33-35].

Declaration of interest

All authors are employees of Applied Biology, Inc. the manufacturer of Photocil. The paper was funded by Applied Biology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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