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Is Narrowband UVB Phototherapy in Combination With Nonsteroidal Topical Medications More Effective at Repigmentation of Vitiligo Lesions When Compared to Narrowband UVB Therapy Alone in Healthy Men and Women Between the Ages of 11 and 69?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not narrowband UVB (NB-UVB) phototherapy in combination with nonsteroidal topical medications is more effective at repigmentation of vitiligo lesions when compared to NB-UVB therapy alone in healthy men and women between the ages of 11 and 69.

STUDY DESIGN: Review of three peer-reviewed randomized controlled trials written in English, two of which were published in 2014, and one in 2011.

DATA SOURCES: Studies were selected based on the method of study, the randomized- control structure of the studies, and the relevance to the clinical question, and all were identified as patient-oriented evidence that matters (POEMS).

OUTCOMES MEASURED: A variety of methods were used to evaluate the outcomes of treatment, including visual analog scale (VAS), Patient Global Assessment (PGA), Investigator Global Assessment (IGA), Visitrak™, palm thumb method, vitiligo scoring index (VASI), and the Lund and Browder (L & B) index.

RESULTS: Three different nonsteroidal topicals were used in conjunction with NB-UVB, calcipotriol, tetracycline, and 0.1% tacrolimus ointment. Of these three topicals, only 0.1% tacrolimus ointment in combination with NB-UVB was shown to have a significant result, with a 13.1% reduction in lesions and a *P* value of 0.005, indicating a difference when compared to NB-UVB therapy alone. The *P* values for the other two studies were very similar, with values of 0.557, and 0.566, suggesting they have no enhancing effect when used with NB-UVB.

CONCLUSION: Two of the three studies analyzed concluded that the addition of a nonsteroidal ointment to NB-UVB was not more effective than NB-UVB alone. The only topical that had statistical support was 0.1% tacrolimus ointment, an immunosuppressive agent, suggesting that this topical enhances treatment outcome when used with NB-UVB. NB-UVB is a gold standard of care for the treatment of generalized vitiligo. Immunosuppressive agents, such as tacrolimus, when added benefit patients by decreasing a larger area of depigmentation. Further research is warranted to obtain a better understanding of the role of nonsteroidal immunosuppressive ointments in vitiligo treatment.

KEY WORDS: vitiligo, NB-UVB, topical tetracycline, tacrolimus

INTRODUCTION

Vitiligo is an acquired skin disorder that results in macules and patches of depigmentation most commonly found on sun-exposed areas of skin. Vitiligo is autoimmune in nature, as the melanocytes, the cells that produce the skin's pigment, are destroyed. Vitiligo affects 1% of the world's population, with generalized vitiligo (vitiligo vulgaris) being the most common; it is symmetric in distribution and widespread throughout the body. Other types of vitiligo include acrofacial (extensor surfaces and orifices), segmental, focal, mucosal, and universal. Vitiligo affects all age groups and races but most often erupts in childhood and early adulthood. Vitiligo is asymptomatic, but its unsightly appearance draws patients to seek medical advice and treatment. Interestingly, vitiligo is associated with many other autoimmune disorders, including hypothyroidism, alopecia areata, and Addison's disease. Its degree of heritability is approximately 30%. Some have hypothesized that it is brought on by stress, trauma, or even sunburn, but none of these causes have been confirmed. Vitiligo is typically a clinical diagnosis, but a skin biopsy can be completed for a definitive diagnosis. Although vitiligo currently has no cure, several treatment options are available.

Annually, an average of 1.8 million people visit physician offices with concerns pertaining to vitiligo, 39,000 seek treatment from hospital outpatient departments, and 137 million dollars are spent on patients with vitiligo. [1] Vitiligo causes psychological anguish in patients, as they are singled out for looking different. Skin condition is crucial for both mental and physiological well-being because it influences relationships, occupation, and self-esteem. In some cultures, patients with vitiligo are completely ostracized. For example, Indian culture regards vitiligo as Sweta Kustha, meaning, "white leprosy." [2] Thus, continued research on more effective treatment options is invaluable to these patients.

Some popular treatment modalities used include ultraviolet light (sometimes used in combination with other therapies), corticosteroids, calcineurin inhibitors, excimer lasers/lamps, and cosmetic interventions. Ultraviolet radiation, particularly NB-UVB, has shown great promise for those who have extensive generalized vitiligo, and numerous studies have shown that it is more effective and has less of a side effect profile when compared to ultraviolet A therapy (PUVA). This type of treatment is time consuming, however, requiring patients to visit their physician's office an average of 3 times a week for 6 to12 months. Corticosteroids, on the other hand, are usually considered first line when lesions are limited (< 10% body surface area [BSA]); however, this has to be monitored closely because of the risk of skin atrophy. Calcineurin inhibitors, such as tacrolimus and pimecrolimus, are topicals that do not cause skin atrophy and are particularly useful when treating vitiligo on the face. Research has begun to look at their efficacy when used in combination with UVB light and laser treatments, and results are promising. Evidence regarding other nonsteroidal ointments, such as topical vitamin D analogs (calcipotriol), is less convincing partly as a result of lack of research. Few studies have looked at its potential when used in combination with NB-UVB therapy. Another modality, the excimer lamp/laser, is used for small areas of vitiligo but has not shown superiority to UBV light. Finally, cosmetic camouflage using dye/pigment preparations can be used for those who do not want medical intervention. All of these interventions have been proved in at least one setting to decrease the area of depigmentation in patients with vitiligo. Steroids are typically first line, but because of the high incidence of skin atrophy, an alternative nonsteroidal is being investigated. NB-UVB is considered a standard of care, but because it is time consuming, a combined therapy with nonsteroidal ointment may be able to cut down on light therapy sessions.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not NB-UVB phototherapy in combination with nonsteroidal topical medications is more effective at repigmentation of vitiligo when compared to NB-UVB therapy alone in healthy men and women between the ages of 11 and 69 years.

METHODS

The criteria for selection included that the population consist of healthy male participants and healthy female participants who were not pregnant. Participants also had to be older than age 11 years and younger than age 69 years and classified as having stable generalized vitiligo. Patients also must not have had recent prior treatment. Only randomized controlled right/left comparative trials that compared NB-UVB therapy in combination with a nonsteroidal medicated ointment on one side of the patient's body compared to controlled groups of NB-UVB therapy alone or in combination with a placebo ointment on the opposite side of that same patient's body. The nonsteroidal adjunctive therapy included tacrolimus 0.1% ointment, calcipotriol ointment, and tetracycline ointment. The outcome was based on the repigmentation of vitiligo lesions. The studies by Nordal and Kalafi, utilized tacrolimus and tetracycline, respectively, were randomized, controlled, and double blind. [3,4] The study by Khuller, which analyzed calcipotriol, was a right/ left prospective comparative trial that did not use a placebo ointment and was not double blind.[5]

In order to find ideal articles, the keywords used included vitiligo, NB-UVB, topical tetracycline, and tacrolimus. These keywords were researched by the author using PubMed in December 2014. All articles were randomized controlled trials, published in English and peer-reviewed, and were selected based on the clinical relevance concerning NB-UVB therapy in

combination with a nonsteroidal with an appropriate control side of NB-UVB alone or with placebo ointment. Articles especially needed to address the patients' concerns with the size of depigmented lesions in generalized vitiligo. Each study was highly selective regarding inclusion and exclusion criteria listed in Table 1. Articles were excluded if published before the year 2000, if participants were younger than 11 or older than 69 years old, if PUVA was used, or if studies contained a steroidal topical. Statistical values of interest included *P* values, mean change from baseline, confidence intervals, absolute benefit increase (ABI), relative benefit increase (RBI), and number needed to treat (NNT).

Table 1: Demographics and characteristics of included studies

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Kalafi, 2014 [3]	Randomized controlled double-blind placebo study	30	11-66	Generalized, stable vitiligo (nonprogressive or no new lesions in the previous 3 months)	Pregnant or lactating patients, children < 8 years old, photodermatoses or cutaneous malignancy, used other medications for vitiligo in the previous 3 months	0	Topical tetracycline on one side vs. Vaseline placebo on the other side twice per day, NB-UVB therapy 2-3 times per week for 12 weeks.
Khullar, 2014[4]	Randomized right-left prospective comparative clinical trial	27	12-60	Male or female aged 12-60 years, 5-50% of body surface area, stable or slowly progressive disease, B/L symmetrical patches; no topical treatment in last 2 weeks or systemic treatment in previous 4 weeks	Pts with segmental, universal, palmo-plantar, or mucosal vitiligo, photosensitivity dermatoses, immunosuppression, impaired liver or renal function, hypercalcemia or hypercalciuria Urolithiasis, concomitant use of medications affecting calcium metabolism, pregnant or lactating women	2	Half of body topical calcipotriol applied twice/day + NB-UVB therapy (TIW) vs. UVB therapy alone on opposite site for 24 weeks

Nordal, 2011[5]	Randomized controlled trial	46	23-69	> 18 yrs old Fitzpatrick skin type II-VI Symmetric	Pregnant and breast feeding	6	Tacrolimus 0.1% ointment on one side of body and Protopic base placebo ointment on opposite side every night+NB-UVB 3times/ week for 3 mos with 3 mo f/u

OUTCOMES MEASURED

All three studies used slightly different measurements, but all revolved around patient-centered concerns regarding the area of depigmentation. The Kalafi study used the VASI score, a clinician-used index that measures percent depigmentation, where scores were broken down as follows: 100% = total depigmentation, 90% = speck of pigmentation, 75% = more depigmented areas than pigmented areas, 50% = equal pigmented and depigmented areas, 25% = more pigmented areas than depigmented areas, and 10% = specks of depigmentation.[4] The Khuller study used a combination of L&B index score, a chart that measures BSA affected; IGA, a subjective reading by the investigator that uses a scale from -1-5 with -1 indicating worsening and 5 indicating 100% repigmentation; and PGA, a subjective reading from the patient ranging from 1-10, with 10 indicating maximum disease at baseline. The Nordal study employed the VAS, a subjective measure by patients on the impact of living with vitiligo. Visitrak^{TM} was used to obtain an objective measure of vitiligo target lesions. Data from Visitrak$^{TM\ was}$ converted to dichotomous data and regarded patients with 20% reduction in depigmentation compared to placebo as "high responders," those with less percentage depigmentation considered "low responders," and those with the same results on both sides considered "non-responders."

RESULTS

Study 1. In a study by Kalafi, 30 patients at an outpatient dermatology office with generalized and stable vitiligo were selected to participate. Patients were instructed to use tetracycline ointment twice a day on one side and a Vaseline-based placebo on the opposite side in the same amount and position. All participants received NB-UVB 2 to 3 times per week, and data for analysis were collected during the 12th week using VASI. The study gave all values of pre- and post-VASI scores for both groups. Thus, to convert these points into dichotomous data, a patient was considered to have benefitted significantly from treatment if there was a 25% decrease in the area of depigmentation. This method showed that only 1 patient from the treatment side and 1 patient from the placebo side showed significant improvement. There was a significant change from baseline on both sides, with both sides reporting a *P* value of 0.026; however, when the treatment and control side were compared against one another, the *P* value was recorded as 0.566 (Table 2). The article referred to successful cases as patients who demonstrated any improvement from baseline, stating that 16.6% of patients who used tetracycline showed improvement. Likewise, 16.6% of patients who used NB-UVB alone showed a degree of improvement. The only adverse effect recorded was stinging at the site of application, but data were not provided, so number needed to harm (NNH) was not calculated. The NNT calculation resulted in an error message because both treatment modalities had exactly the same effect.

Table 2: Kalafi study: Topical tetracycline + NB-UVB (experiment) vs. NB-UVB alone (control)

CER (control event rate)	EER (experiment event rate)	Relative Benefit Increase (RBI)	Absolute Benefit increase (ABI)	Numbers Needed to Treat (NNT)	*P* value
3%	3%	0	0	N/A- no difference between tx	0.566

**P* value was only considered significant if < 0.05.

Study 2. Khuller instituted a right/left prospective comparative trial that consisted of 25 patients, including both male and female participants aged 12 to60 years with 5 to50% of BSA affected, stable, bilateral symmetrical patches, and no use of topical treatment for previous 2 weeks or systemic therapy for 4 weeks. The study was randomized as to which side received treatment, but was not double blind. Calcipotriol ointment was applied twice per day at night and 2 hours after UVB therapy, which was completed 3 times per week. This study used various modalities, including L&B index score, IGA, and PGA, to look at change in pigmentation that was of particular interest. PGA data were collected but not published; therefore, the IGA scores were transformed into dichotomous data, where patient outcome was considered significant if a 50% or greater increase in repigmentation occurred (Table 3). Forty-four percent of patients saw 50% or greater increase in repigmentation on the treatment side; likewise, 44% of patients also demonstrated 50% or more increase in repigmentation on the placebo side. The L&B index score, IGA *P* values, and PGA *P* values were 0.577, 0.821, and 0.706, respectively, and not significant. The mean change from baseline for the NB-UVB side alone collected from the three measurement modalities were 51.4 +/- 28.1 (95% CI 39.8-63), 2.7 +/- 0.5 (95% CI 2.0-3.4), and 5.6 +/- 3.4 (95% CI 4.3-7.0), respectively. The mean changes on the on the calcipotriol side included 49.0 +/- 24.5 (95% CI 38.9-59.1), 2.5 +/- 0.4 (95% CI 2.0-3.3), and 5.8 +/- 3.2 (95% CI 4.4-7.1). Furthermore, repigmentation did not occur earlier in one group than the other, and pigment matching to the individual's skin color was the same in both groups. Repigmentation onset was between 3 to10 weeks on both sides, and the difference in onset was not statistically significant, *P* value = 0.533. Collectively, the data are consistent in that treatment in both groups was statistically similar. Calcipotriol induced numerous adverse reactions, including erythema,

xerosios, pruritis, and folliculitis. Nevertheless, an adverse profile of NB-UVB alone was not presented; thus, NNH was not calculated.

Table 3. Khuller study: Calipotriol + NB-UVB (experiment) vs. NB-UVB alone (control)

CER (control event rate)	EER (experiment event rate)	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)	*P*-Value for IGA scores	*P*-Value for PGA scores	*P*-Value for L&B	Repigmentation onset measured in weeks
44%	44%	0	0	N/A- no difference in treatment	0.821	0.706	0.557	0.533

**P* value considered significant if < 0.05

Study 3. The study conducted by Nordal researched the usefulness of adding a 0.1% tacrolimus ointment to NB-UVB therapy using a randomized right/left, double-blind, comparative study. Forty patients were recruited from a dermatology practice at a university hospital. Pregnant and breast-feeding patients were excluded likely because tacrolimus is a category C drug. Ointments were distributed symmetrically every night for 3 months, and NB-UVB therapy was completed 2 to3 times per week with a 3-month follow-up. The data that were presented in the study focused on target lesion measurements using Visitrack™; those with 20% improvement compared to placebo side were considered high responders (9 participants), those with less improvement were considered low responders (19 participants), and the rest were considered nonresponders. Overall, there was a median 42.1% decrease in target lesions on the tacrolimus side as compared to a median of 29% decrease on the placebo side, with a statistical *P* value of 0.005 (Table 4). Please note that the data presented within the study could not be converted into a dichotomous form; thus, ABI, RBI, and NNT could not be calculated. The study also mentions a direct correlation between an increase in the reduction in target lesion and an increase in the number of tacrolimus applications; however, this correlation was not seen with an increase in NB-UVB

treatments. Although subjective scores using VAS were not published, researchers noted that patients with even minimal improvement responded positively while receiving treatment. Perioral dermatitis on the tacrolimus side was observed, but no data were published in the study; therefore, NNH could not be calculated.

Table 4: Nordal study: Percent reduction in target lesions of vitiligo Tacrolimus 0.1% +NB-UVB 0.1% VS. placebo + NB-UVB

Median % reduction of NB UVB + Tacrolimus	Median % reduction of NB-UVB + Placebo	Difference	*P* value
42.1	29.0	13.1	0.005

**P* value considered significant if < 0.05

DISCUSSION

The goal of this systematic review was to determine if nonsteroidal ointments in combination with NB-UVB therapy is more beneficial in the treatment of vitiligo than treatment with NB-UVB alone. Vitiligo is a highly treatment-resistant condition, and often one modality does not suffice. NB-UVB has much support in the literature, thus reinforcing its efficacy in treating generalized vitiligo; however, adjunctive therapies other than topical steroids are less recognized. Steroid creams have long been a go-to option for clinicians and patients, but they have a significant side effect profile; therefore, looking into other medicated ointments would be worthwhile.

Of the 3 nonsteroidal ointments studied, only tacrolimus (0.1%) ointment appears to have an enhancing effect when used with NB-UVB. Tacrolimus is a calcineurin inhibitor, an immunosuppressant, and blocks the release of inflammatory cytokines. Tacrolimus is commonly prescribed to treat atopic dermatitis, although it recently has gained attention for its potential to treat psoriasis, pyoderma gangrenosum, lichen planus, and vitiligo. A black-box warning on the product reports weak linkage between tacrolimus use and malignancy (skin and lymphoma); thus, the manufacturers recommend short-term and minimal use. This contradicts the previous

misconception that a nonsteroidal would be a better option for long-term topical application, especially when tacrolimus quantity and length of use seem to have a direct benefit on vitiligo. Nonetheless, more research needs to be completed to obtain a better understanding of the association. Topical tetracycline (indicated for impetigo and perioral dermatitis) and calcipotriol (indicated for plaque psoriasis) have safer profiles, but after analyzing both studies, they appear to have no benefit when used as an adjunctive therapy.

Larger studies need to be performed; the studies included in this review were limited with 40, 30, and 25 participants. Also, the quality of the Khullar study was undesirable because it was not double blind and did not utilize a placebo ointment. The study was also male dominant with a 4:1 ratio, did not include an age range of participants, and included 3 acrofacial types of vitiligo, while this review focused on the generalized vitiligo type. The study also focused on darker skin types III-V. The Kalafi study exclusively looked at Fitzpatrick skin type III and included adolescents and children in the study aged 11-17 years. The Nordal study looked exclusively at adults, predominantly women, and the majority of patients studied were Fitzpatrick skin type III (22 participants), IV (11 participants), V (1 participant), and VI (1 participant). The sites of application varied widely among the three studies, including the knees, arms, face, neck, and trunk; each study looked at a combination of these sites. This may be significant because sources have identified that tacrolimus may be most beneficial for the head and neck.[6] Ideally, studies would consist of equal gender, consist of adults or children exclusively, consist of an array of skin types with race included, and focus on a certain anatomical site. As a result of the many discrepancies across these topics, these results cannot be generalized to everyone, only to those mentioned in the respective studies.

CONCLUSION

After review of the 3 studies, the benefit of nonsteroidals as an adjunctive therapy is inconclusive. All three nonsteroidal were chosen because they have a mechanism that has potential to induce repigmentation. Calcipotriol activates a pathway to stimulate melanocyte production; whereas tetracycline and tacrolimus reduce inflammatory cytokines. Tacrolimus was the only successful therapy in enhancing the effects of NB-UVB. This systemic review was intended to be broad to work as a starting point for future research. Since tacrolimus had the most promise, a look at different calcineurin inhibitors would be interesting to see if one has more of an enhancing effect with NB-UVB than the others, thus potentially lessening phototherapy sessions and long-term corticosteroid use. Before additional research in this area can begin, however, more research concerning the association between tacrolimus and malignancy, specifically analyzing quantities and time frames in which risk is likely to occur must be completed. Future studies can improve the knowledge base on this topic by focusing on a wide range of skin pigment types, specifying a pediatric or adult study, and focusing on specific anatomical sites.

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