Study of the Enhanced Role of Latanoprost Combined with Narrow Band Ultraviolet B Rays in Vitiligo Repigmentation

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Abstract

Background:Vitiligo is an acquired, autoimmune disease characterized by depigmented macules and patches on the skin, which occur secondary to melanocyte destruction. Focal and segmental vitiligo patterns involve ≤10% body surface area (BSA) and are considered stable patterns. Generalized vitiligo typically involves ≥10% BSA, appears bilaterally in a symmetric distribution, and generally follows a relapsing and remitting disease course. The pathogenesis is complex and involves the interplay of multiple factors; however, the exact pathogenesis is not well known. In particular, the autoimmune mechanism is clearly established. Vitiligo may appear at any age and affect both sexes.Treatment can be challenging, though available modalities of therapy include pharmacologic, surgical, and phototherapy. Appropriate characterization of vitiligo type, consideration of disease extent and duration, and efficacy of prior therapies can guide management and maximize treatment efficacy.Latanoprost was documented to stimulate prostaglandin E2(PGE2) formation, and repigmentation is likely to be induced in part by endogenous PGE2 which acts as a melanogenic stimulator.Narrow band UVB rays are one of the safest and most effective therapeutic modalities of vitiligo. It emits wavelengths between 310 and 315 nm. This specific wavelength is very effective in vitiligo because it can stimulate the dormant skin melanocytes and also modulate the cutaneous immune system.

Keywords: Vitiligo, Latanoprost,Narrow Band Ultraviolet

1.Introduction:

Vitiligo, a common depigmenting skin disorder, has an estimated prevalence of 0.5-2% of the population worldwide. The disease is characterized by the selective loss of melanocytes which results in typical nonscaly, chalky-white macules. In recent years, considerable progress has been made in our understanding of the pathogenesis of vitiligo which is now clearly classified as an autoimmune disease. Vitiligo is often dismissed as a cosmetic problem, although its effects can be psychologically devastating, often with a considerable burden on daily life. In 2011, an international consensus classified segmental vitiligo separately from all other forms of vitiligo, and the term vitiligo was defined to designate all forms of nonsegmental vitiligo. This review summarizes the current knowledge on vitiligo and attempts to give an overview of the future in vitiligo treatment**(1).**

2. Topical Therapies

Topical corticosteroids are effective agents in vitiligo due to their immunosuppressive and anti-inflammatory properties. Super-potent or potent corticosteroids are appropriate for treating the

trunk and extremities, whereas mid-potency topical corticosteroids (or topical calcineurin inhibitors) are better suited for the face, neck, or intertriginous regions and in children. Cyclical application (1 week on and 1 week off for 6 months or for 5 days on and 2 days off) can help avoid the cumulative adverse effects of topical corticosteroids, including skin atrophy, telangiectasias, and steroid-induced acne. **(2)** Treatment should not exceed 14 days in a month per package insert**(3).**

Topical calcineurin inhibitors, such as tacrolimus (0.1%) or pimecrolimus (1%), are immunomodulatory, steroid-sparing agents that may be used anywhere with the exception of mucous membranes, and are nearly as effective as topical corticosteroids but more favorable with steroid-sparing properties**(4).** Twice daily use can promote disease stabilization and twice weekly applications may be considered for maintenance therapy**(5).** Topical calcineurin inhibitors may be used in combination with topical corticosteroids on 'off' days. Although tacrolimus poses a theoretical, long-term risk of carcinogenicity due to its immunosuppressive properties, no cases in humans have been reported**(5).**

In a mouse model investigating dermal photocarcinogenicity, topical 0.1% tacrolimus was associated with the development of lymphoma. An intra-individual left-right comparison study by Ostovari et al. involving 9 patients with generalized vitiligo found that repigmentation was optimized when topical calcineurin inhibitors were combined with UVB (308 nm excimer laser) exposure in all patients, whereas no repigmentation was observed on the side treated with topical 0.1% tacrolimus alone. **(7).**
Vitamin D analogs, such as topical calcipotriene, used in combination with phototherapy, may reduce time to repigmentation and the overall cumulative dose delivered**(8).**

3. Role of Narrow Band Ultraviolet B Rays In Vitiligo
Narrow band UVB rays are one of the safest and most effective therapeutic modalities of vitiligo. Narrow band UVB was first used in vitiligo in 1997 by Westerhof and Nieuweboer-Krobotova. It emits wavelengths between 310 and 315 nm**(9).**

The peak emission is at 311 nm and this ensures reduction of superfluous radiation, consequently minimizing the risk of severe burning or other cutaneous side effects of UV radiation. This specific wavelength is very effective in vitiligo because it can stimulate the dormant skin melanocytes and also modulate the cutaneous immune system **(9).**

Mechanism of action of NBUV B in vitiligo:
1. **Immunomodulation**
Vitiligo is characterized by 2 stages: the active stage in which there is ongoing destruction of melanocytes by immune cells, and the stable stage in which the depigmented skin lesions remain constant over time. In the active stage of vitiligo, the main mechanism of NB-UVB phototherapy may be explained by its immunomodulatory actions. Narrow band UVB may stimulate epidermal expression of IL-10, which induces differentiation of T-regulatory lymphocytes that can inhibit the activity of autoreactive T lymphocytes. It has also been shown to induce apoptosis of T cells in psoriatic skin lesions, and a similar mechanism may occur in vitiligo **(10).**

Besides inducing apoptosis, NB-UVB treatment lowered the production of proinflammatory cytokines such as IL-1α, IL-2, IL-5 and IL-6, whereas the synthesis of anti-inflammatory IL-10 was significantly augmented. Furthermore, NB-UVB also decreased the number of epidermal Langerhans cells **(11)**.

2. Migration of melanocytes from the outer hair root sheath

Active melanocytes are usually identified by their expression of melanocyte-specific proteins; however, melanocyte precursors are more difficult to be detected, as they do not produce melanin and therefore do not usually express those specific proteins. So in vitiligo lesional skin, there is a selective loss of active melanocytes in the epidermis, while the inactive/immature melanocytes in hair follicles are spared **(12)**.

In the stable stage of vitiligo, the major repigmentation effect of NB-UVB may be due to stimulation of functional melanocytes in the perilesional skin or immature melanocytes in hair follicles. This effect has been described as "biostimulation." Therefore NB-UVB enhances activation and functional development of immature melanocytes in the outer root sheath of hair follicles. The upward migration of melanocytes from the outer root sheath to the epidermis leads to the commonly observed formation of perifollicular pigmentation islands **(13)**.

3. Stimulation of basic fibroblast growth factor

Studies have shown that NB-UVB irradiation increased the expression of endothelin 1 and basic FGF by keratinocytes, which in turn may promote melanocyte proliferation. Moreover, it has been demonstrated that NB-UVB irradiation may induce phosphorylated focal adhesion kinase (FAK) expression and matrix metalloproteinase 2 activities in melanocytes, leading to increased melanocyte migration. Therefore, NB-UVB phototherapy may promote vitiligo repigmentation directly by increasing melanocyte mobility and indirectly by inducing melanocyte-related growth factors from keratinocytes **(14)**.

4. Role of NB-UVB on Vitamin-D

Molecular studies showed that Vitamin D modulates cellular level melanogenesis by the induction of tyrosinase enzyme and promotes the production of melanin by immature melanocytes in the bulge region **(15)**.

In vitiligo pathogenesis, the effect of the calcium imbalance, vitamin-D recertor-APa-1 polymorphism and low circulatory levels of 25-OH Vitamin D has been implicated. Patients with vitiligo have been noted to have lower expression of vitamin D receptor and also lower serum

levels of vitamin D when compared with a control population **(16)**.

Later on, authors have proposed that cumulative doses of NB-UVB could improve low vitamin D and this in turn may influence the rate of repigmentation**(17)**.

5. Reduction of oxidative stress

(18) reported that there are higher levels of erythrocyte malonyldialdehyde (MDA) and lower levels of SOD and erythrocyte glutathione peroxidase (GSH-Px), seen in patients before NB-UVB treatment which indicated the remarkable imbalance in the oxidant–antioxidant system among patients with vitiligo in favour of oxidant mechanisms. This imbalance could play a substantial role in disease pathogenesis. Authors reported also that the use of NB-UVB

phototherapy for 6 months has been shown to be associated withsignificant improvement in oxidant–antioxidant imbalance, stated by reduction in MDA levels and an increase in GSH-Px levels.

Addition of oral antioxidants to ongoing therapy has been shown to potentiate the beneficial effects of NB-UVB phototherapy on repigmentation and oxidant–antioxidant imbalance (**12**).

6. Stimulation of stem cells

Narrow band UVB has also been shown to directly stimulate hair follicle-derived neural crest stem cells to differentiate into melanocyte lineage, as well as increased melanin formation and tyrosinase expression (**19**).

4. LATANOPROST

Prostaglandins are potent lipid hormones that trigger multiple pathways, leading to cellular growth, differentiation and apoptosis regulation. Keratinocytes release PGs shortly after exposure of the skin to UV radiation and these hormones are also present in   chronic inflammatory lesions of the skin (**20**).

Ultra violet rays activate melanogenesis as it causes membrane phospholipids to breakdown via COX enzyme action on arachidonic acid. Through upregulation of phospholipase activity and COX-2 production, PGE2 and PGF2α production is inducible by UVR and one or more of these products may provide the activation signal of melanogenesis. These PGs have several receptors such as PGE2 receptors, i.e., type 1 PGE2 (EP1) and type 3 PGE2 (EP3) and PGF2 α receptors (FP) which have been expressed by melanocytes (**21**).

Latanoprost solution is one of PGF2 α analogues, normally used in the treatment of glaucoma as a topical treatment for ocular hypertension through intraocular pressure reduction. Since the evidence of its periocular and iridal pigmentation side effects, latanoprost has been evaluated for the treatment of cutaneous hypo-pigmentation, showing to be effective especially in combination with different therapies (e.g: phototherapy) (**22**).
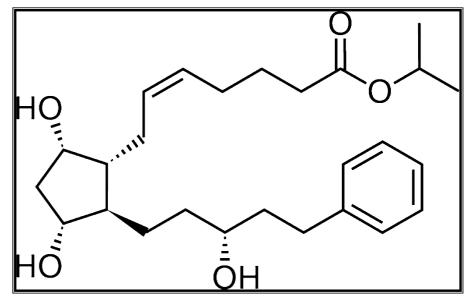

Figure (1): Pharmacological structure of latanoprost (**23**).

The role of PGs in melanogenesis and mechanism of action:

The effects of PGs on keratinocytes are complex and include proliferation stimulation and/or inhibition, differentiation stimulation and apoptosis regulation. The complexity of the keratinocyte response to PGs is partly caused by the complexity of the PGs receptors. The PGE2 receptors consist of four related receptors (EP1–EP4), which are divided into a group that have a high affinity for PGE 2 (EP3, EP4) and a group with low affinity (EP1, EP2) **(20)**.

The PGF2α actions are mediated with FP receptors, which is coupled with G -protein and its stimulation leads to activation of the turnover of phospholipase C-induced phosphoinositide, intra cellular $Ca2 +$ mobilization, activation of mitogen-protein kinase and the activation of the protein kinase C **(24)**.

It has been shown that PGF2α, and to a lesser extent PGE2, act as potent triggers for human melanocyte dendricity. Latanoprost has been found to stimulate the activity of tyrosinase in human melanocytes without affecting their proliferation **(20).**

In addition, it was reported that in human melanocytes PGE2 and PGF2**α** do not increase adenosine monophosphate (cAMP). Subsequently, the mechanism used to mediate melanocyte dendrite formation by PGE2 and PGF2 **α** is a cAMP-independent although the cAMP / protein kinase A (PKA) pathway is the most characterized pathway responsible for melanocyte dendrite formation **(25).**

Each EP1, EP3 and FP receptor has been shown to signal via phospholipase C (PLC) in human platelets. Prostaglandin E2 and PGF2 **α** can therefore via the pathway of PLC-protein kinase C regulate melanocyte dendricity**(26).** Alternatively, there is a second messenger system that controls cytoskeletal protein and can be used to mediate the melanocyte dendricity, for example Endothelin 1, a potent triggering factor for melanocyte dendricity through increased intracellular Ca2 **(27).**

The receptors EP1/EP3 and FP could potentially stimulate melanocyte dendricity through PLC dependent mechanisms. The operative event in this pathway is the hydrolysis of the membrane lipid phosphoinsotide 4, 5-bisphosphate (PIP2) into inositol 1, 4, 5-trisphosphate (IP3) and diacylglycerol (DAG) through PLC. As PIP2 serves as a binding site for various proteins binding to and/or modify actin; its hydrolysis allows   for actin binding proteins to be translocated from PIP2 and incorporated into the cytoskeleton in areas of active actin reorganization which is essential for dendricity**(28).** Tyrosinase activity regulation is complex and may occur via post-translation activation of the enzyme, including phosphorylation and N-linked glycosylation that alters enzyme activity or stability via increased enzymes expression at the message level or both mechanisms potentially **(14).**

There is another possible mechanism that is based on p53 is possible for the observed increase in tyrosinase activity and expression after latanoprost. There is evidence of an increase in tyrosinase synthesis through UV dependent p53 up regulation **(29).**

In vitiligo repigmentation, all of the previous mechanisms may play a positive role. Furthermore, latanoprost was documented to stimulate PGE2 formation, and repigmentation is likely to be

induced in part by endogenous PGE2 which acts as a melanogenic stimulator. Prostaglandin E2 also has other biologic activities, it increases the formation of tonofilaments and keratohyalin in keratinocytes and it blocks the processing/presenting function of Langerhans cells in skin **(30).**

A study of 24 vitiligo vulgaris patients compared the effect of latanoprost versus tacrolimus ointment and both combined with NBUVB and microneedling. It was reported that none of the patients showed any side effects and the lesions treated with latanoprost generally responded to pigment production better than tacrolimus ointment, although the difference was not statistically significant. At the end of treatment, the number of lesions with >75% pigment production on latanoprost was significantly higher than control lesions **(22).**

The efficacy of topical latanoprost as a monotherapy for vitiligo was previously reported by **Parsad et al.**, **(31)** and **Kapooret al.**, **(32)**. Later on,**Anbar et al.**, **(23)** confirmed that latanoprost 0.005% solution is more effective than NB-UVB and the combination of both treatments gives enhanced response.

It has been reported that combination of latanoprost with other methods of vitiligo treatment is more effective than its use as monotherapy. A group of 30 patients with vitiligo received a combination of FraxelHerbium laser, topical latanoprost solution and focused UVA1 laser and they demonstrated good clinical results in term of repigmentation rate with no side effects mentioned. All the patients were satisfied by the protocol treatments, not only for the achieved aesthetical results but also for its limited number of sessions **(21).**

Nowroozpoor et al., **(33)** demonstrated that latanoprost had significantly better outcome regarding improvement of the disease and repigmentation than placebo. No specific adverse effect or complication was observed in the groups treated with it. However, **Kim et al., (34)** has mentioned some adverse effects of latanoprost with its use in skin like diffuse facial hyperpigmentation.

The effect of combination of latanoprost with NBUVB rays **(35, 36, 32 and 23):**
In contrast to those treated with NB-UVB alone, a considerable improvement has been observed in lesions treated with combination of latanoprost and NB-UVB, this may be explained by;
Firstly, NB-UVB stimulates in situ release of PGs, improving the additive pigmentation of the exogenous latanoprost added.

The second suggestion is the synergistic influence on exposure to NB-UVB by other mediators, for instance, endothelin 1, alpha-melanocyte-stimulating hormone (αMSH), adrenocorticotropichormone (ACTH), SCF and nerve growth factor (NGF) with the applied latanoprost.

Thirdly, NB-UVB exposure not only induces PGF2 **α** synthesis in melanocyte, but also upregulates the expression of FP receptors, enabling the exogenous latanoprost to add further influence.

Other applications of PGF2 α analogues in dermatology:

Eye lashes hypotrichosis

Prostaglandin F receptors are expressed in eyelash hair follicles in the dermal papilla and outer root sheath. These receptors are the target of latanoprost and hypertrichosis could be induced by several mechanisms. Studies reported that the average time needed to induce hypertrichosis varies from 2 or 3 days to several weeks **(37).** However, **Stecchi et al., (38)** showed no hypertrichotic effect in patients who had applied latanoprost for 6 months.

Androgenic alopecia

Khidhir et al., (39) examined the effects of bimatoprost on cultivated scalps and found that follicular growth rate; number of anagen follicle and total hair development were concentration-dependently increased. This effect was refuted by a PGF2 **α** receptor antagonist, verifying a direct receptor-medicated mechanism

.

Prostaglandin F2 **α** analogs are well suited to target androgenic alopecia by lengthening the phase of anagen follicles and stimulating resting follicles into anagen. Increased hair density has been demonstrated in a small number of patients **(40).**

Alopecia areata:

The use of PGF2 **α** analogs has been more thoroughly investigated in alopecia areata, primarily of the eyebrows and eyelashes in cases of alopecia areata universalis, but results of topical latanoprost and bimatoprost in these cases were unremarkable. The immune-mediated nature of the disease and the alteration in anagen function or duration are the possible causes of these unremarkable results **(40).**

A randomized comparative study of the efficacy of topical latanoprost versus topical betamethasone diproprionate lotion in the treatment of localized alopecia areata study has shown that topical latanoprost solution is less effective than topical betamethasone dipropionate lotion. The results of this study are in accordance with other studies that have also reported lesser efficacy of latanoprost in promoting hair regrowth in patients with eyelash and eyebrow alopecia areata **(41).**

In another study, bimatoprost was shown to be more effective than topical mometasone furoate cream in the treatment of localized alopecia areata. This could be explained by the fact that the steroid which was used in the study (mometasone furoate) is of lesser potency than the topical steroid used in the previous study (betamethasone propionate), hence explaining better results with betamethasone **(42).**

9. Conflict of Interest: Noconflictofinterest.

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