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Photo (Chemo) Therapy and Vitiligo

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Abstract

Background: Vitiligo is an acquired idiopathic pigmentary skin disorder characterized by sharply demarcated milky white macules with variable size and shape. It has an estimated worldwide incidence of 0.5-4% and occurs in half of the patients before the age of 20 years. Since exact pathogenic mechanism is unknown, several proposed hypotheses are alternation of cellular and humoral immunity, melanocyte damage stimulated by chemicals released from nerve endings, structural aberration of melanocytes, melanocytorrhagia, epidermal cytokines, metabolic dysregulations and convergence theory depended on combination of these etiologic factors. Treatment of vitiligo depends on viable melanocyte reservoirs which induce repigmentation during various therapies. Although melanocyte reservoir mainly shown as hair follicle unit, repigmentation arise from three main sources. These are hair follicle unit, melanocytes located at the edge of vitiligo lesion and unaffected melanocytes within areas of depigmented epidermis. Treatment modalities for vitiligo therapy divided in three main groups as medical therapy, phototherapy and surgical therapy. Vitiligo lesions should be initially treated with topical medical therapy or localized phototherapy. If depigmentation is larger than 10-20% of body surface area, systemic medical therapy or phototherapy should be sought. When depigmentations do not regress in spite of appropriate interventions, surgical therapies should be considered as the lesions become refrectory and stable. In this review, we discuss the literature and evidence base for phototherapy in vitiligo and summarized previous studies.

Introduction

Vitiligo is an acquired idiopathic pigmentary skin disorder characterized by sharply demarcated milky white macules with variable size and shape. It has an estimated worldwide incidence of 0.5-4% and it occurs in half of patients before the age of 20 years [**1, 2**]. The family history is positive in approximately 20-30% of patients and it affects all races, skin types and ethnicities [**3**]. Genetic data support a non-Mendelian, multi-factorial, polygenetic inheritance [**4**].

Studies conducted to enlighten etiology of vitiligo for several decades. There are numerous studies published about varied pathogenic mechanisms involved in pigmentation loss but beyond these studies unknown mechanism are yet to be determined. Since exact pathogenic mechanism is unknown, several proposed hypotheses are alternation of cellular and humoral immunity [**5, 6**], presence of metabolic defects in melanocytes themselves or in the epidermal melanin unit leading to oxidative stress, neuronal theory depended on melanocyte damage stimulated by chemicals released from nerve endings [**7**], structural aberration of melanocytes [**8**], melanocytorrhagia [**9**], epidermal cytokines, [**10**] lack of melanocyte growth factors, metabolic dysregulations [**11**] and convergence theory depended on combi-

nation of these etiologic factors [**12**]. Recent studies conducted about genetic association of etiologic factors and various gene regions have been proposed. All of these data suggests that genetically affected individuals are prone to melanocyte damage, which conclude with high immune response targeting to melanocytes antigens.

Several classification systems have been proposed in literature. These classifications based on the distribution or localization of the depigmented lesions. Most frequently used classification consist of 3 major types: localized vitiligo with focal, segmental and mucosal subtypes, generalized vitiligo with acrofasial, vulgar and mixed subtypes and universal vitiligo. In addition to this classification, two forms of vitiligo described for therapeutic evaluation: non-segmental (bilateral) vitiligo with chronic, progressive and unpredictable course, where immune alternations mainstay of pathogenesis, and segmental (unilateral) vitiligo with an early age at onset, short course of disease where stabilization and no further progress is frequently seen.

Most of early studies report that fully depigmented vitiligo skin characterized microscopically by the complete absence of melanocytes [**13**]. But in a recent study by *Tobin* et al. melanocytes were isolated and established in vitro from lesional skin even if they couldn't demonstrate immunohistochemically any intact melanocyes. They also observed small amounts of mature melanin granules in the amelanotic skin of vitiligo even up to 25 years of disease duration. They implied that some partially functioning melanocytes must be retained in inter-follicular vitiligo skin, as it is not possible melanin could be transferred from outside the lesion [**2**]

Treatment of vitiligo depends on viable melanocytes reservoirs which induce repigmentation during various therapies. Although melanocyte reservoir mainly shown as hair follicle unit, repigmentation arise from three main sources. These are hair follicle unit, melanocytes located at the edge of vitiligo lesion and as *Tobin* et al. mentioned before unaffected melanocytes within areas of depigmented epidermis [**14**]. Since predominant repigmentation arises from hair follicle, extensive research has been undertaken to study mechanism of follicular repigmentation. In 1959, *Staricco* showed amelanotic melanocytes in the external root sheath of hair follicles that suggested immature pigment cell [**15**]. Further studies with psoralens and UVA (PUVA), demonstrated DOPA negative, non-dendritic pigment cells along the external root sheath of hair follicle which migrated towards the basal cell layer to become mature, dendritic, tyrozinase positive melanocytes in vitiligo lesion [**16**]. In 1991, *Cui* et al. investigated role of hair follicles in the repigmentation and implied that treatments in vitiligo stimulate inactive melanocytes in the middle and/or lower parts of hair follicle to proliferate and migrate long the outer root sheath to the nearby epidermis, where pigment cells expanded radially and clinically observed as perifollicular repigmentation [**17**]. Later on, in 1996, *Grichnik* et al. documented the presence of small, dendritic, tyrosinase negative and c-kit positive melanocytes found mostly around follicular ostium, suggesting a source of epidermal repigmentation [**18**]. Last decade various studies conducted about melanocyte and hair follicle stem cells. In 2002, *Nishimura* et al. identified melanocyte stem cell in the lower permanent portion of Dct-lacZ transgenetic mice hair follicles which activated at early anagen phase as they coupled to the hair generating cycle [**19**]. Further studies showed that, melanocytes stem cells located in the lower part of the hair follicle bulge, just below the hair follicle stem cells [**20**]. The bulge region of the hair follicle described as outer root sheath of the hair follicle at the insertion site of arrector pili muscle. Recent studies showed that, the bulge region was a relative immune privilege, protecting the hair follicle epithelial stem cell reservoir from autoaggressive immune attacks [**21**]. These data suggest that immature melanocytes at different stages of development in bulge region may be stimulated to induce repigmentation in vitiligo lesion. Besides these melanocyte reservoirs, intact melanocytes at borders of depigmented lesions may also reproduce and migrate to lesional skin as another source of melanocytes.

Since melanocyte reservoirs reside in different structures of skin, the repigmentation patterns changed due to source of melanocytes. These patterns include perifollicular, diffuse, marginal and combined pattern. *Parsad* et al. documented repigmentation patterns of

Table 1. Oral PUVA Therapy in Vitiligo

S. no	Therapy	Study	No. of Pts.	Repigmentation %	Remarks
1.	Topical PUVA versus NB UVB	Westerhof et al., 1997[59]	281	Grup I (Topical PUVA(28)or NB UVB (78)) Grup II(311-nm UVB), Grup I 13/28 (46%) Topical PUVA, 52/78 (67%) NB UVB showed repigmentation after 4 months, Grup II >75% repigmentation; after 3 months 5/60 (8%), after 12 months 32/51 (63%)	Intervention study
2.	PUVA	Şahin et al., 1999[66]	33	28/33 (84%) some improvement, 12/33 (36%) 51-75%, 6/33 (18.2%) >75% repigmentation	Retrospective
3.	Calcipotriol	Ameen et al., 2001[67]	22	30-100% improvoment 17/22 (77%)	Open study
	versus Calcipotriol & PUVA		4	good reponse 3/4(75%)	
4.	Calcipotriol & PUVA (Do not response PUVA)	Yalçın et al., 2001[68]	21	76-100% excellent (1/21), 51-75% good (5/21), 26-50% moderate (5/21), 10-25% poor (4/21), no response (5/21)	Prospective trial
5.	PUVA & Calcipotriol versus PUVA & Placebo	Ermis et al., 2001[69]	35	C+PUVA statistically significant difference favoring calcipotriol, C+PUVA seems safe and effective	Placebo-controlled, double-blind, right/left comparative
6.	PUVA	Cherif et al., 2003[70]	23	no response 11/23, minimal 12/23, moderate and marked 0/23	Prospective
	versus Calcipotriol & PUVA			no response 7/23, minimal 9/23, moderate 7/23, marked 0/23 (PUVA+C faster than PUVA)	
7.	PUVA versus Calcipotriol & PUVA	Baysal et al., 2003[71]	22	C+PUVA didnt lead to significant increase in response rate compared PUVA alone	Right/left comparative, open study
8.	Topical Khellin & UVA	Valkova et al., 2004[53]	17	3/16 (18.8%) 90-100% repigm., 4/16 (25%) 60-80% repigm., 9/16 (56.2%) 20-50% repigm., KUVA AND PUVA similiar improvement	Pilot study
	versus PUVA		16	2/17 (11.8%) 90-100% repigm., 7/17 (41.2%) 60-80% repigm., 7/17 (41.2%) 20-50% repigm., 1/17 (5.8%) no repigm.	
9.	PUVA versus NB UVB	Yones et al., 2007[72]	25 25	>50% imrovement 9/25 (36%) PUVA >50% imrovement 16/25 (64%) NB UVB, NB UVB therapy superior to oral PUVA	Randomized, double-blind trial

Table 2. NB UVB Therapy in Vitiligo

S.no	Therapy	Study	No. of Pts.	Repigmentation %	Remarks
1.	NB UVB	Njoo et al., 2000[73]	51	42/51 (82%) >25%, 27/51(53%) >75% repigm., best response (>75%) face (72%) and trunk (74%)	Open and uncontrolled
2.	NB UVB	Scherschun et al., 2001[74]	11	5/7 >75% repigm., 1/7 50% repigm., 1/7 40% repigm., NB UVB useful and well-tolerated treatment for vitiligo	Retrospective review
3.	NB UVB & Topical pseudeocatalase	Patel et al., 2002[75]	32	Has not been shown to be effective	An open, single-centre study
4.	NB UVB		13	25/27 (92%) repigmentation, NB UVB effective treatment for vitiligo	
	versus NB UVB & Folic Acid & Vitamin B12	Tjioe et al., 2002[76]	14	Not shown any advantage from adding Vitamin B12 and Folic Acid	Controlled study
5.	Calcipotriol & NB UVB	Dogra et al., 2003[77]	case report	Calcipotriol & NB UVB therapy > placebo & NB UVB	Case report
6.	NB UVB	Yashar et al., 2003[78]	77	30/71 significant (66-100%), 17/71 moderate (26-65%), 16/71 mild (10-25%), 8/71 minimal/no response	Retrospectively review
7.	NB UVB & Tacrolimus 0.1%	Castendo-Cazares et al., 2003[79]	case report	Tacrolimus act synergistically with UVB	Case report
8.	NB UVB	Natta et al., 2003[80]	60	25/60 >50% repigm. face, trunk, arms and legs, <25% repigm. hand and foot lesion	Retrospective analysis, open study
9.	NB UVB (Parametric Modeling)	Hamzavi et al., 2004[81]	22	The effect of NB UVB on vitiligo repigmentation highly significant	Prospective, randomized, controlled
10.	Calcipotriol & NB UVB	Kullavanijaya and Lim, 2004[82]	20	66-100% significant 8/17 (47%), 26-65% moderate 6/17 (35%), 10-25% mild 1/17 (6%), <%10 minimal 2/17 (12%)	An open, bilateral comparative study
11.	Calcipotriol & NB UVB	Ada et al., 2005[83]	20	NB UVB acceptable repigm. 55% of pts., excellent repigm. 15% of pts., adding calcipotriol not increas the efficacy	Prospective, single-blinded, right/left comparison clinical study
12.	NB UVB	Kanwar et al., 2005[84]	14	10/14 (71.4%) marked to complate (75-100%), 2/14 (14.3%) moderate (50-75%) or mild (<50%) repigm., effective and well-tolerated	Open, uncontrolled
13.	NB UVB	Goktas et al., 2006[85]	24	Left - 8/24 (33.3%) earlier onset repigm.	Prospective, right/left comparison clinical study
	versus Calcipotriol & NB UVB			Right - 16/24(66.7%) earlier onset repigm., effective and work faster than NB-UVB alone	
14.	NB UVB	Arca et al., 2006[86]	25	Mean repigmentation percentage 41.6 +/- 19.4%	Prospective, randomized, comparative study
	Versus Calcipotriol & NB UVB		15	Mean repigmentation percentage 45.01 +/- 19.15%, No statistically significant difference in two groups.	
15.	NB UVB & Topical catalase and superoxide dismutase	Kostovic et al., 2007[87]	22	>50% 11/19 (57.9%), 26-50% 6/19 (31.58%), 1-25% 1/19 (5.26%), no repigm 1/19 (5.26%)	Multicenter, double-blinded, placebo controlled

Table 2. NB UVB Therapy in Vitiligo (Continued)

S.no	Therapy	Study	No. of Pts.	Repigmentation %	Remarks
16.	NB UVB	Bhatnagar et al., 2007[88]	25	Mean degree of remigmentation 67.57% (excluding therapy resistant sites)	
	Versus PUVA		25	Mean degree of remigmentation 54.2% (excluding therapy resistant sites)	
17.	NB UVB activated topical pseudocatalase	Schallreuter et al., 2008[89]	71	Effective in treatment for childhood vitiligo, >75% repigm. 66/71 face/neck, 48/61 trunk, 40/55 extremites	Uncontrolled, retrospective
18.	NB UVB				
	versus NB UVB & Topical catalase superoxide dismutase	Yüksel et al., 2009[90]	30	No statistically significant difference	Preliminary study
19.	NB UVB & Pimecrolimus 1%	Esfandiarpour et al., 2009[91]	50	NB UVB & Pimecrolimus 1% increases efficacy and probably hasten the response only facial vitiligo other anatomical areas wasn't statisticlly significant	Randomized, double-blind, placebo-controlled
	versus NB UVB & placebo				
20.	NB UVB & Topical pseudeocatalase	Bakis-Petsoglou et al., 2009[92]	14	NB UVB moderately effective, pseudocatalase cream doesn't appear to add any incremental benefit to NB UVB alone	Randomized, double-blinded, placebo-controlled trial
	NB UVB & Placebo		18		
21.	NB UVB	Majid et., 2010[93]	90	62% mean repigm. (VASI score of 3.60)	Prospective, half and half comparison study
	versus NB UVB & topical plasental extract			63% mean repigm (VASI score of 3.69), placental extract statistically insignificant effect on the efficacy of NB UVB	
22.	NB UVB	Elgoweini and El Din, 2009[94]	24	55.6% repigmentation	Open, randomised, non-observer blinded
	versus NB UVB & Oral Antioxidants (Vitamin E)			72.7% repigmentation	
23.	NB UVB	Gamil et al., 2010[95]	20	No significant difference between both sides	Open, bilateral comparative study
	versus Calcipotriol & NB UVB				
24.	NB UVB home	Wind et al., 2010[96]	64	Home 57/64 (80%)	Retrospectively questionary study
	versus NB UVB outpatient		60	Outpatient 32/40 (86%), no significant difference	
25.	NB UVB	Kumar et al., 2009[97]	150	73/150 25-75% repigmentation, 51/15 <25% repigmentation, NB UVB effective and safe tool management of vitiligo	Prospective, open, non-randomized
26.	NBUVB	Sapam et al., 2012[98]	28	0% repigm. 0 patient, 1-25% repigm. 4 patients, 26-50% repigm. 15 patients, 51-75% repigm. 8 patients, 76-100% repigm. 0 patient	Observer blinded, randomized study
	Versus PUVA		28	0% repigm. 0 patient, 1-25% repigm. 3 patients, 26-50% repigm. 20 patients, 51-75% repigm. 3 patients, 76-100% repigm. 0 patient	

Table 3. Microphototherapy in Vitiligo

S. no	Therapy	Study	No. of Pts.	Repigmentation %	Remarks
1.	NB UVB microphototherapy	Menchini et al., 2003[60]	734	510/734 (69.48%) >75% treated areas, BIOSKIN UVB microphototherapy seems highly effective in restoring pigmentation	Open study
2.	NB UVB microphototherapy	Akar et al., 2009[99]	32	4/32 (12.5%) visible repigmentation, safe but therapeutic effectiveness is limited	Retrospective study
3.	BB UVB microphototherapy	Welsh et al., 2009[61]	12	Face(66.25%) good to exclellent response, neck, trunk, genitalia (31.5%) moderate response, extremites no response	Open, prospective clinical trial

Table 4. NBUVB Comparative Studies in Vitiligo

S.no	Therapy	Study	No. of Pts.	Repigmentation %	Remarks
1.	NB UVB versus Topical PUVA	Westerhof et al., 1997[59]	281	Grup I(Topical PUVA(28) or NB UVB (78)) Grup II(311-nm UVB), Grup I 13/28 (46%) Topical PUVA, 52/78 (67%) NB UVB showed repigmentation after 4 months, Grup II >75% repigmentation; after 3 months 5/60 (8%), after 12 months 32/51 (63%)	Intervention study
2.	NB UVB	Yones et al., 2007[72]	25	>50% imrovement 16/25 (64%) NB UVB, NB UVB therapy superior to oral PUVA	Randomized, double-blind trial
	versus PUVA		25	>50% imrovement 9/25 (36%) PUVA	
3.	NB UVB	Bhatnagar et al., 2007[88]	25	Mean degree of remigmentation 67.57% (excluding therapy resistant sites)	Open, randomised, non-observer blinded
	versus PUVA		25	Mean degree of remigmentation 54.2% (excluding therapy resistant sites)	
4.	NB UVB	Casacci et al., 2007[100]	16	Excellent repigm. (76-100%) 1/16 lesion (6%), good repigm. (51-75%) 5/16 lesion (31%)	Randomized, investigator blinded, half side comparary
	versus Monochromatic Excimer Light (308 nm)			Excellent repigm. (76-100%) 6/16 lesion (37.5%), good repigm. (51-75%) 4/16 lesion (25%)	
5.	NB UVB versus Excimer Laser	Yang et al., 2010[23]	51	Repigm. NB UVB 42.2%, 308 nm excimer laser 51.3%, repigm. patterns to location, age, duration of lesions and speed response similarities both NB UVB and 308 nm excimer laser	Randomized, open prospective study
6.	NBUVB	Sapam et al., 2012[98]	28	0% repigm. 0 patient, 1-25% repigm. 4 patients, 26-50% repigm. 15 patients, 51-75% repigm. 8 patients, 76-100% repigm. 0 patient	Observer blinded, randomized study
	versus PUVA		28	0% repigm. 0 patient, 1-25% repigm. 3 patients, 26-50% repigm. 20 patients, 51-75% repigm. 3 patients, 76-100% repigm. 0 patient	
7.	NBUVB	El-Zawahry et al., 2012	20	Good response 1 patient, moderate response 4 patients, poor response 12 patients, widening in 3 patients	Prospective, randomized, controlled comparative study
	Versus UVA1		20	Excellent response 1 patient, very good response 5 patients, good response 7 patient, moderate response 3 patients, poor response 4 patients	

352 vitiligo patches in 125 patients after various treatments. They implied that vitiligo lesions repigment with different patterns depending on the type of treatment given. Of the 352 vitiligo patches, 194 (55%) showed predominant perifollicular repigmentation. PUVA predominantly exhibits a perifollicular pattern (127; 65.5% in systemic PUVA, 35; 18% in topical PUVA). They also observed diffuse pigmentation in 98 patches (27.8%) of which 66 (67.3%) were on topical steroids, marginal repigmentation in 15 patches, of which majority (80%) were on systemic PUVA and topical calcipotriol [**22**]. In a recent study conducted by *Yang* et al., narrow-band ultraviolet B (NBUVB) and excimer laser used in vitiligo treatment to evaluate repigmentation patterns. The most frequent repigmetation pattern was perifollicular pattern and these findings were similar to previous study [**23**].

Anatomic location and affected skin area are important features of vitiligo to decide most proper treatment for the patients. Vitiligo lesions have diverse responds due to anotomic location. Face and the neck have the maximum repigmentation response. Proximal extremities and trunk respond effectively but not as well as facial skin. Lastly, in acral parts of the extremities repigmentation is difficult to achieve. The variable amount of hair follicle unit and melanocytes in diverse skin areas could explain this repigmentation difference.

In this review, we present an update about phototherapy for vitiligo. Treatment modalities for vitiligo therapy divided in three main groups as medical therapy, phototherapy and surgical therapy. Vitiligo lesions should be initially treated with topical medical therapy or localized phototherapy. If depigmentation is larger than 10-20% of body surface area, systemic medical therapy or phototherapy should be sought. When depigmentations do not regress in spite of appropriate interventions, surgical therapies should be considered as the lesions become refrectory and stable.

Ultraviolet Radiation

Ultraviolet radiation (UVR) is widely used in various dermatologic condition since second half of 20th century. UVR is an electromagnetic radiation with a wavelength shorter than visible light, but longer than x-rays with three main spectra: UVC (200-290 nm), UVB (290-320 nm), and UVA (320-400 nm). Over the past decades, the development of irradiation devices with selective emission spectra has led to an outstanding role for phototherapy in the treatment of skin condition. In 1982, a selective emission spectra known as UVA1 (340-400 nm) introduced and used safetly in many skin conditions. In 1988, the Philips TL01 fluorescent lamb, emitting a narrow UV radiation at 311/312 nm (NBUVB) introduced and used safely in the treatment of vitiligo patients. Today it is known that, UVA, UVB and NBUVB are essential treatment options for vitiligo affecting more than 10-20% of the skin surface [**24**].

UVR shows its effects in two main ways in vitiligo treatment. UVR has immunosuppressive effects which help to reduce autoimmune condition that leads melanocyte destruction. The immunosuppressive effects of UVR are mediated mostly by the middle wave length range 290-320 nm. Therefore, the vast majority of photoimmunologic studies utilized UVB [**25**]. There is also recent evidence that UVA can affect the immune system. *Iwai* et al. showed that UVA irradiation dose dependently decreased the ability of epidermal cells to present antigen to T cells directly and modulate Langerhans cell function at least partially via an oxidative pathway [**26**] UVR reduce the number of Langerhans cells and impair their capacity to present antigens, [**25**] stimulates keratinocytes to release immunosuppressive soluble mediators including interleukin (IL)-10 [**27**] and other contributing mediators as tumor necrosis factor-α (TNF-α), [**28**] IL-4, prostaglandin E2, [**29**] calcitonin gene related peptide [**30**], α melanocyte stimulating hormone [**31**], and platelet activating factor [**32**], induce reactive oxygen species that contribute to impairment of the function of antigen presenting cells [**25**] and induce T-regulatory cell activity [**33**]. *El-Ghorr* and *Norval* compared immunosuppressve effects of NBUVB and broad-band UVB. They mentioned that NBUVB has relatively more suppressive effects than broad-band UVB on systemic immune responses [**34**]. This difference could be explained by variable cytokine responses due to UVR spectra.

On the other hand, UVR stimulates melanocytes proliferation and migration which

provide repigmentation of affected skin. *Moretti* et al. investigated the role of cytokine production of epidermal microenvironment in vitiligo lesions. They documented that a significantly lower expression of GM-CSF, stem cell factor (SCF), and basic fibroblast growth factor (bFGF) in lesional skin compared with unaffected skin and suggested that epidermal microenvironment may be involved in vitiligo [**10**]. According to this study, *Wu* et al. showed that, sera from patients after PUVA treatment contained higher levels of bFGF, SCF and hepatocyte growth factor as compared with healthy controls and patients with active vitiligo, which may create a favorable environment for melanocytes to survive [**35**]. In another study *Wu* et al. investigated affects of NBUVB on melanocytes proliferation in vitro and they observed a significant increase in bFGF and in endothelin-1 (ET-1) release as bFGF is a natural mitogen for melanocytes and ET-1 can stimulate DNA synthesis in melanocytes. They also suggested that matrix metalloproteinase-2 (MMP-2) activity play important roles in narrow-band UVB-induced migration of melanocytes [**36**]. In a recent study, *Starner* et al. showed that UVR radiation stimulates prostoglandin E2 (PGE2) secretion in melanocytes that leads cAMP production, tyrosinase activity and proliferation in melanocytes [**37**].

UVR reduce autoimmune condition that leads melanocyte destruction and create a favorable environment for melanocytes proliferation. According to studies conducted by *Osawa* et al. it could be suggested that activation of stem cells in the hair follicle and interfollicular epidermis that partially escape the immune destruction mechanism by not expressing melanocyte differentiation markers could provide differentiated melanocytes for repigmentation in a favorable environment utilized by UVR [**38**].

PHOTOCHEMOTHERAPY

Photochemotherapy is an effective therapeutic option for vitiligo which is utilized by combination of photosensitizers and UVA. The most common form of photochemotherapy is consist of topical psoralens (P) and UVA combination which is called PUVA [**24**]. PUVA therapy can be used three different ways in vitiligo treatment. These are oral psoralen plus UVA (Oral PUVA), topical psoralen plus UVA (Topical PUVA) and topical psoralen plus solar UVA (PUVAsol). Other common forms of photochemotherapy are including khellin plus UVA and phenylalanine plus UVA.

Oral PUVA

Oral PUVA therapy consists of having the patient receive total body UVA (320-400 nm) irradiation 2-3 times a week with 0.25-2 Joules per cm2 (J/cm2) after taking a photosensitizer which is usually 8-methoxypsoralen (8-MOP). Patients take medication 1-2 hours before irradiation generally at a dose of 0.2-0.6 mg/kg. Irradiation dose increased according to the patients' response and patients must wear UVA blocking glasses for 18 to 24 hours after ingestion of 8-MOP [**39, 40, 41**]. After treatment, patients should apply a broad spectrum sunscreen to exposed areas and avoid unnecessary sun exposure. It is ill-advised to treat children younger than 12 years with oral PUVA therapy because of side-effects on the long-term [**41**]. Bath PUVA therapy may provide a wider margin of safety in pediatric patients with lower UVA radiation and minimal systemic psoralen absorption [**42**].

Contraindications for oral PUVA treatment include ocular defects such as cataracts or retinal disease, abnormal liver function and photosensitivity disorders. Results of various studies conducted by oral PUVA in vitiligo treatment demonstrated below (**Table 1**). Complications of oral PUVA treatment include acute side effects and potential long-term risks. Acute side effects consist of drug intolerance reactions and side effects of combined action of psoralen plus UVA radiation. These are nausea and vomiting as drug intolerance reactions and increased delayed erythema reactions, severe burning, fever, general malaise, pruritus, stinging pain, polymorphous light eruption-like rashes, acne-like eruptions, subungual hemorrhages and hypertrichosis as combined action of psoralen with UVA radiation [**24**].

Potential long-term risks are chronic actinic damage, carcinogenesis and ophthalmologic effects. PUVA lentiginosis results from repeated and prolonged treatment. There is no risk

of cutaneous melanoma associated with these lentigines. Cutaneous carcinogenicity is the major concern for long-term PUVA treatment [**24**]. Although *Stern* et al. documented that oral PUVA therapy is associated with a persistent, dose-related increase in the risk of squamous cell cancer [**43**], similar documentation has not occurred in patients with vitiligo expect two case reports [**44, 45, 46**] *Halder* et al. investigated cutaneous malignancies in 326 patients treated with PUVA for vitiligo and failed to document actinic keratoses or skin cancer during an observation period of 4 years [**47**]. Before beginning PUVA therapy it is essential to avoid prolonged treatment and educate patients to protect from unnecessary sun exposure.

Topical PUVA

Topical PUVA therapy administrated by application of 0.1-0.01% 8-methoxy-psoralen ointment vitiliginous area 15 to 30 minute before UVA irradiation at a dose of 0.12-0.25 J/cm2 , 1-3 times weekly with increment of 0.12 J/cm2/week according to patient's skin type. After asymptomatic mild erythema appears, the irradiation dose can be maintened at a level sufficient to retain erythema [**41**].

Grimes et al. investigated effectiveness of topical PUVA treatment in 73 patients. They observed 100% repigmentation in 7 patients (9%), 50% or greater repigmentation in 26 patients(36%), less than 50% repigmentation in 29 patients (40%), and no repigmentation in 11 patients (15%). These repigmentations obtained from various anatomic sites treated: 56% of facial lesions; 35% of trunk areas; 36% of the extremities [**48**].

PUVAsol

PUVAsol therapy is a modification of topical PUVA therapy in which natural sunlight used as the light source. In this therapy, patients applied 0.001% 8-methoxy-psoralen ointment in vitiliginous area 30 minutes before exposure to the sun. Vitiliginous area then exposed to sunlight 15-20 minutes. Duration of exposure should be increased 5 min per treatment until developing slight erythema. After treatment patient should wash treated sites and apply a broad-spectrum sunscreen [**40**]. Although PUVAsol therapy is easy to apply and cost-effective, sun overexposure and inadequate therapy parameters make this therapy unreliable.

Khellin

Khellin (Khe), a naturally occurring furochromone isolated from the seeds of Ammi visnaga is used systemically or topically with UVA or natural sunlight in the treatment of vitiligo. It has a chemical structure and photobiologic and phototherapeutic properties similar to psoralens. In addition to these similarities, it is though that khellin plus UVA (KUVA) treatment has no adverse phototoxic and carcinogenetic side effects due to lower number of cross links with DNA than PUVA treatment [**49**] *Carli* et al. demonstrated that KUVA treatment stimulates melanocytes proliferation and melanogenesis in vitro [**50**]. KUVA treatment initiated with an oral dose of 50-100 mg khellin given 2 hours before UVA exposure from 5 to 15 J/cm2 according to patient's skin type [**51**].

Several studies published to enlighten effectiveness of Khe in the treatment of vitiligo. *Hofer* et al. conducted a retrospective study in 28 patients with KUVA therapy. They achieved >70% repigmentation in 17 patients after a mean of 194 treatments. They emphasized that no skin cancers or actinic damage of vitiliginous skin were found in any patient after a mean of 40 months follow up [**52**]. More recently, in a pilot study, *Valkova* et al. compared PUVA and KUVA therapy in 33 patients and they achieved similar results in both therapy. In addition to this conclusion, they emphasized that KUVA requires longer duration of treatment and higher UVA irradiation than PUVA therapy [**53**]. In a recent review article, Falabella and Barona share their clinical outcome after topical Khe therapy with 3% Khe emulsion plus 5-10 min of daily sunlight exposure. They achieved remarkable repigmentation properties over a period of several months, particularly on facial and neck lesions and without side effects. They also suggested that controlled, double blind, randomized studies should be done to establish the efficacy of this therapy [**51**].

Phenylalanine

Phenylalanine is an essential amino acid which is a precursor for tyrosine. Tyrosine converted to melanin by tyrosinase in melanocytes. It has been shown that pigmentation in the human epidermis depends on the autocrine synthesis of L-tyrosine from L-phenylalanine (Phe) by phenylalanine hydroxylase (PAH) in melanocytes [**54**]. PAH activities increase linearly with inherited skin color yielding eightfold more activities in black skin compared to white skin. L-phenylalanine uptake and turnover in the melanocytes is vital for initiation of melanogenesis and regulated by calcium [**55**].

Several studies conducted to determine effectiveness of topical or systemic phenylalanine with UV irradiation in the treatment of vitiligo. Phe is used in a dose of 50 mg/kg, 30 min to 1 h before 2-12 J/cm2 UVA exposure (PAUVA) [**39, 56**] *Camacho* and *Mazuecos* performed a non-controlled retrospective survey of a group of 193 patients treated with oral (50-100 mg/kg day) and topical (10% gel) phenylalanine plus 30 minutes of sun exposure. When the study closed, they achieved 100% repigmentation in 122 patients (84.1%) on the face, 35 (35.7%) on the trunk, and 33 (21.1%) on the limbs [**57**]. After 3 years, they modified this therapy by adding 0.025% clobetasol propionate and performed an open trial on a group of 70 patients. They reported that 68.5% of patients achieve an improvement of 75% or more [**58**]. *Siddiqui* et al. conducted an open trial in 149 patients for 18 months and a small double-blind trial in 32 patients for 6 months. They achieved various grades of repigmentation up to 77% in the open and 60% in the blind trial [**56**].

Contraindications for this treatment include phenylketonuria, pregnancy, breast-feeding, previous arsenic exposure or radiotherapy and autoimmune disorders [**51**]. Although these studies supported effectiveness of phenylalanine in the treatment of vitiligo, this method could only be used when other therapies failed.

PHOTOTHERAPY

NBUVB

Since its introduction in 1988, the Philips TL01 fluorescent lamb, emitting a narrow UV radiation at 311/312 nm (NBUVB) has been used successfully and safely in phototherapy for many skin diseases especially psoriasis. After a decade, in 1997, *Westerhof* and *Nieuweboer-Krobotova* describe NBUVB therapy for vitiligo. They reported that 67% of patients with twice-weekly NBUVB therapy showed repigmentation, compared with only 46% of patients receiving topical PUVA therapy twice-weekly [**59**] In comparision with PUVA, NBUVB therapy does not required oral psoralens and has no ocular or gastrointestinal side effects, is cheaper, can be used in pregnancy and childhood, does not require post-therapy eye protection. NBUVB therapy suggested less carcinogenetic than PUVA although follow-up studies to determine the true carcinogenetic risk are lacking [**24**]

NBUVB therapy started with initial dose at 150-250 mJ/cm2 for 2-3 times weekly followed by 20% increasing weekly due to patient's response. Several studies investigate Results of various studies conducted by NBUVB in vitiligo treatment demonstrated in (**Table 2**).

Targeted UVB microphototherapy

Photo(chemo)therapy widely used in vitiligo affecting more than 10-20% of the skin surface. For patients with localized vitiligo total body irradiation can cause unnecessary UVR overexposure. Targeted UVB microphototherapy could be used in localized vitiligo with UVB irradiation directed only to the lesion. UVB microphototherapy devices have an irradiation spectra 300-320 nm and administrated directly to the lesion 2-3 times per week.

Several studies conducted to evaluate effectiveness of targeted UVB microphototherapy (**Table 3**). *Menchini* et al. used an UVB microphototherapy device that has an irradiation spectra 300-320 nm with 311 nm peak and administrated directly to the lesion 2-3 times per week in 734 patients. They reported that 510 subjects (69.48%) achieved normal pigmentation on more than 75% of the treated areas (112 of these were totally repigmented), 155 subjects (21.12%) achieved 50-75% pigmentation of the treated areas, and 69 (9.40%) showed less than 50% pigmentation. They also mentioned that targeted UVB microphototherapy could represent the treatment

of choice for vitiligo limited to less than 30% of the skin surface [**60**]. In a recent study, *Welsh* et al. used a broad-band UVB-targeted phototherapy device in 12 patients with localized vitiligo (less than 10% body surface) twice per week for 30 sessions. They achieved repigmentation rate with an average of 66.25% on lesions of the face, and of 31.5% on the neck, trunk, and genitalia without any repigmentation in extremities [**61**]. In a randomized double blind study conducted with a small group of patients, *Asawanonda* et al. mentioned that targeted broadband UVB produces similar clinical responses to targeted NB-UVB in the treatment of vitiligo [**62**].

Combination therapies have been used widely in refractory vitiligo lesions. In a recent study, *Lotti* et al. investigated effectiveness of various combination therapies with an UVB microphototherapy device that has an irradiation spectra 300-320 nm with 311 nm peak. They combine this therapy with tacrolimus 0.1% ointment twice a day, pimecrolimus 1% cream twice a day, betamethasone dipropionate 0.05% cream twice a day, calcipotriol ointment 50 microg/g twice a day and 10%l-phenylalanine cream twice a day. They mentioned that 0.05% betamethasone dipropionate cream plus 311-nm narrowband UVB microphototherapy apparently give the highest repigmentation rate.

UVA

UVA irradiation therapy without psoralen has not been studied enough to assay effectiveness in vitiligo treatment. As far as we know, there is only one randomized controlled trial in literature about UVA effectiveness in vitiligo. *El-Mofy* et al. used UVA irradiation without psoralen in 20 patients for 48 sessions over 16 weeks with 15 J/cm2 dosage. They achieve 60% and above repigmentation in 50% of patients and suggested that UVA irradiation without psoralens may be an important therapeutic value in vitiligo [**63**].

UVA therapy without psoralens could also be performed in selective emission spectra known as UVA1 (340-400 nm). UVA1 therapy is categorized in three different dosage regimes as; low dose (20-40 J/cm2), medium dose (40-80 J/cm2) and high dose (80-120 J/cm2) [**64**]. Like other emission spectra of ultraviolet radiation, UVA1 has immunosuppressive effects which help to reduce autoimmune condition that leads melanocyte destruction. UVA1 can induce apoptosis in skin infiltrating leukocytes; suppress proinflammatory cytokines like TNF-α and IL-12, decrease level of IFN-ϒ and ICAM [**65**]. Superior to other phototherapy options, UVA1 is relatively free of side effects like erythema and cellular transformation. In a recent randomized controlled study, *El-Zawahry* et al. compared UVA1 and NB UVB therapy in the treatment of vitiligo. They emphasized that NB UVB was superior to UVA1 which seems to be dose dependent and seems to be of limited value in treatment of vitiligo as a monotherapy [**65**]

Comparison Studies

Recent studies are conducted to compare effectiveness of UVR therapies especially PUVA versus NBUVB. These studies enlighten effectiveness of PUVA versus NBUVB with various repigmentation rates (**Table 4**). According to these studies NBUVB was found to be equally or more effective with less side effects than PUVA therapy.

Because there is no treatment of choice in vitiligo, physicians and patients are confused by vast number of treatment modalities. According to studies and their level of evidence most appropriate studies are conducted on phototherapy in the treatment of vitiligo. In this review we discussed phototherapy in vitiligo and summarized previous studies. These studies suggested PUVA and NBUVB therapy are most appropriate treatment option in lesions larger than 10-20% of body surface area. In comparasion with PUVA, NBUVB does not required oral psoralens, has no ocular or gastrointestinal side effects, can be used in pregnancy and childhood, does not require post-therapy eye protection. By these advantages, NBUVB appear to be better than PUVA therapy.

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