P306 TRAITEMENT DU VITILIGO PAR PHOTOTHÉRAPIE UVB À SPECTRE ÉTROIT (TLO1) EMPLOI D'UN PROTOCOLE AGRESSIF

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Récemment une étude importante a été publiée sur l'emploi de la photothérapie UVB à spectre étroit dans le traitement du vitiligo (Westerhof et coll.). Ces auteurs ont rapporté dans leur série des résultats superposables à ceux de la PUVAthérapie topique.

Matériels et méthodes : 12 patients ont été admis au traitement à ce jour : il s'agit de 5 hommes et 7 femmes, âge moyen 31 (extrême : 6-54): 7 patients appartenaient au phototype IV et 5 au phototype III (selon Fitzpatrick). Dans tous les cas la surface atteinte était supérieure à 20 %; il s'agissait de 10 cas de vitiligo non segmentaire et de 2 cas de vitiligo segmentaire. Nous avons utilisé une rampe équipée avec 14 tubes Philips TL100W/0l. L'émission des lampes, mesurée à l'aide d'un dosimètre UV Meter Waldmann, était de 7 mW/cm2 à 20 cm de distance. Nous avons employé le protocole suivant : dose de départ : 70 % de la valeur de la DEM, poursuite du traitement à raison de deux séances par semaine avec augmentation de 20 % toutes les deux séances, si toléré. En cas de survenue d'érythème léger nous maintenions la dose précédente pendant 4 séances; en cas d'érythème intense le traitement était suspendu pendant une semaine. Au préalable 4 patients (3 femmes et 1 homme, âge 18-45) avaient été traités en suivant le protocole de Westerhof : après trois mois de traitement, ces patients ont changé de protocole et sont passés à notre protocole agressif. Des photographies ont été prises chaque mois, en cours de traitement, pour mieux évaluer le succès thérapeutique.

Résultats : à l'heure actuelle 5 patients suivent le traitement depuis 3 mois, 3 patients depuis 2 mois et 4 depuis 5 mois. Parmi les patients traités par le protocole "agressif" 100 % (4 patients) ont montré des signes de repigmentation satisfaisants (diffus) à 5 mois, 60 % (3 patients) à 3 mois et 2 (66 %) à distance de 2 mois. Parmi les patients traités par le protocole de Westerhof (4 patients au total), dans un seul cas (20 %) une repigmentation initiale a pu être observée, après les trois mois de traitement.

Discussion : le protocole de Westerhof prévoyait une dose de départ de 0,075 J/cm2 avec une augmentation de 20 % toutes les deux séances jusqu'à la survenue de l'erythème. Sur la base de notre expérience ce protocole n'est absolument pas capable d'entraîner la moindre réaction érythémale sur les zones cutanées aclrromiques: parmi les 4 patients qui ont été traités avec ce protocole, dans un seul cas, nous avons pu observer quelques signes de repigmentation. Il faut considerer à ce propos, que nos doses de départ (70 % DEM) se situaient toujours au-dessus de 0,5 J/cm2, voire dix fois plus que les doses initiales du protocole de Westerhof. D'autre part notre protocole "agressif" s'est avéré efficace pour maintenir constamment un érythème à peine perceptible pendant toute la durée du traitement. Les résultats, en terme de repigmentation, ont été assez satisfaisants et très satisfaisants en ce qui concerne la précocité de la réponse au traitement. La suspension momentanée du traitement s'est rendue nécessaire dans un seul cas, à cause de la survenue d'érythème d'intensité moyenne sur les lésions, à la cinquième séance. Chez un enfant de 6 ans, faisant partie du groupe, nous avons obtenu de bons résultats sans le moindre effet secondaire.

Conclusion : La photothérapie UVB à spectre étroit deviendra probablement un des traitements de choix pour obtenir la repigmentation dans le vitiligo, surtout en raison de sa meilleure maniabilité par rapport à la PUVAthérapie. Nos résultats, chez un nombre limité de patients, sont très encourageants mais montrent qu'une conduite suffisamment agressive du traitement est indispensable à l'obtention du succès thérapeutique. Toutefois il s'agit toujours d'une étude ouverte, portant sur un nombre limité de cas, qui doit nous inciter à la prudence. L'inefficacité d'un protocole trop "doux" peut être attribuée à l'insuffisante stimulation pigmentogène et à l'épaississement progressif de la couche cornée.

Références

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Mots-clés : Photothérapie (vitiligo). Vitiligo (photothérapie UVB).

Current state of vitiligo therapy – evidence-based analysis of the literature

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Summary
Vitiligo is a skin disease with a worldwide prevalence ranging from 0.5 % to 4 %. Conservative therapies include photochemotherapy, phototherapy with UVB radiation (broadband UVB 290–320 nm, narrow band UVB 311 nm), systemic steroids and pseudocatalase. Modern therapeutic options include treatment with topical immunomodulators (tacrolimus, pimecrolimus), analogues of vitamin D3, excimer laser and surgery/transplantation. Our analysis compares these therapies for vitiligo and the evidence levels supporting their effectiveness.
Conclusions: The face and neck respond best to all therapeutic approaches, while the acral areas are least responsive. For generalized vitiligo, phototherapy with UVB radiation is most effective with the fewest side effects; PUVA is the second best choice. Topical corticosteroids are the preferred drugs for localized vitiligo. They may be replaced by topical immunomodulators which display comparable effectiveness and fewer side effects. The effectiveness of vitamin D analogues is controversial with limited data. Surgical therapy can be very successful, but requires an experienced surgeon and is very demanding of time and facilities, thus limiting its widespread use. L-phenylalanine therapy appears effective on the face but enjoys neither widespread use nor extensive data support. No single therapy for vitiligo can be regarded as the most effective as the success of each treatment modality depends on the type and location of vitiligo.

Introduction
Vitiligo is a skin disease featuring depigmented macules. These often appear symmetrically, usually in the face, but also on the nape, axillae, elbows, hands, knees and genitals. Vitiligo usually occurs in a localized or generalized pattern, as well as rarely in a dermatome. Vitiligo can run a rapidly progressive course or remain stationary. Epidermal and mucosal variants occur. Prevalence ranges from 0.1–4 %. Onset of vitiligo is usually in childhood or in young adults (20–30 years of age); in about 30 % there is a positive family history, so that a genetic component is likely. The health risk presented by vitiligo is the emotional impact on the patient due to disfigurement.

Pathogenesis
The cause of vitiligo is not yet fully understood. It is clear that in affected skin there is a lack of functional melanocytes. Several hypotheses as to the pathogenesis of vitiligo exist, none of which can fully explain the disease. Four hypotheses are of particular importance [1]:

1. One of the most important and well-known theories is the "*autoimmune hypothesis*". It is based on the observation that several autoimmune diseases (e.g. autoimmune thyroid disease, type I diabetes mellitus) often appear along with vitiligo. Further, vitiligo patients often display elevated serum levels of antibodies towards melanocytic antigens (e.g. tyrosinase, tyrosinase-related proteins 1 and 2).
2. The "*neural hypothesis*" presumes that altered reactions of melanocytes

towards neuropeptides, catecholamines and their metabolites are responsible for melanocyte destruction. In depigmented skin, close contact between melanocytes and nerve endings rarely seen in normal skin can be found. In addition, degenerated and regenerated autonomous nerve fibers and thickened basement membranes of Schwann cells are present in the center and at the periphery of depigmented skin lesions. Nerve endings at such sites reveal aberrations in the expression of nerve growth factor (NGF) and neuropeptides.

3. According to the "*self-destruct hypothesis*" melanocytes destroy themselves due to defects in protective mechanisms removing toxic melanin precursors. These defects lead to accumulation of indole derivatives and free radicals which are melanotoxic.
4. The "*biochemical hypothesis*" assumes over-synthesis of hydrobiopterin, a cofactor of tyrosine hydroxylase, resulting in increased catecholamine synthesis. This, too, results in an increase of reactive oxygen species (ROS) toxic for melanocytes. Further, reduced levels of catalase combined with higher concentrations of H_2O_2 have been found in affected and unaffected skin of vitiligo patients.

Treatment modalities

On the basis of these hypotheses different treatment strategies have been devised to restore the functional integrity of epidermis and melanocytes by reactivating residual melanocytes in or stimulating melanocytes in neighboring skin or proliferating hair follicles to migrate into affected areas. Further, some treatments, such as corticosteroids, aim to suppress the immune reaction. All treatments are first presented in overview. Conservative treatments are photochemotherapy, phototherapy with UVB (broad band, bb) or narrow band UVB (311 nm, narrow band, nb) and topical – with rapid progression and great emotional impact even systemic – corticosteroids. Photochemotherapy consists of a combination of psoralens (mainly 8-methoxypsoralen, 8-MOP, PUVA) or khellin (KUVA) with UVA irradiation. Psoralens can be applied topically or administered systemically, khellin only topically due to hepatotoxicity [2]. The principle behind topical pseudocatalase is the enzymatic degradation of H_2O_2 and the resulting reduction of elevated H_2O_2 concentrations; it has not yet been well studied. New hope has been awakened by modern therapies such as topical immunomodulators (TIM) with substances such as tacrolimus or pimecrolimus. Synthetic vitamin D_3 analogues such as calcipotriol can also be applied. Another treatment option is the excimer laser (308 nm xenon chloride laser). Surgical procedures include grafting of autologous melanocytes cultured *in vitro* or skin grafting. A further bur rarely used treatment option is systemic or topical L-phenylalanine.

All treatment options have limited success. This is often quite dependent on course and location of vitiligo. Another problem in evaluating treatment efficacy is the present availability of studies (usually uncontrolled pilot studies and case reports, few randomized controlled studies [randomized controlled trials, RCTs]). It is therefore impossible to name one single treatment modality as the most effective for a particular form of vitiligo. In the following, the abovementioned treatment modalities are assigned evidence levels on the basis of current literature.

Methods

The majority of literature for this review was obtained by a search of the MEDLINE data bank. Selection of publications was done using the following criteria: Studies and reviews should have as high an evidence level as possible, non-systematic and unclear publications were not considered. This paper limits itself to frequently employed and relatively well-studied treatments. Of the available 65 references, 30 (5 of which were RCTs) were actually included.

In assessing success of repigmentation, a statement in percent was made with the value corresponding to the proportion of repigmented skin in the entire affected skin area.

Results

The results of the publications taken into consideration are summarized in Table 1. Studies are arranged in the type of therapy and in decreasing order according to evidence levels.

Photochemotherapy

Photosensitizers used in photochemotherapy (psoralen or khellin) increase the sensitivity of the skin or melanocytes, respectively by, for example, activation of melanocytes or melanosomes as well as induction of IL-1 synthesis. One study shows topical KUVA and systemic PUVA therapy leading to similar responses [3]. These end responses were achieved by PUVA in a statistically significant shorter treatment period ($t = 15.5$, $p < 0.001$) as topical KUVA therapy (Table 2).

Two randomized placebo-controlled trials showed significantly more rapid and strong repigmentation for combined PUVA and calcipotriol therapy [4, 5]. Side effects were slight irritation, erythema and/or pruritus. A study comparing PUVA with UVB-nb showed UVB-nb to be superior after four months; one-fifth more patients showed repigmentation [6]. A retrospective analysis over ten years showed that PUVA resulted in repigmentation over 90 % in only 8 % of patients (usually inhomogeneous and weak repigmentation) [7].

Phototherapy (UVB)

For mono-phototherapy of active, generalized vitiligo, UVB-nb or –bb should be employed, with UVB-nb appearing more effective [8]. On the one hand, phototherapy inhibits the induction and secretion of cytokines as well as apoptosis, on the other, inactive melanocytes in the outer root sheath of hair follicles are stimulated to proliferate and migrate into vitiligo lesions [2]. The combination of UVB and calcipotriol showed no increase in efficacy, probably due to the fact that most of calcipotriol (> 90 %) is degraded by UV irradiation [9]. Burning, pruritus and xerodermia are known side effects.

Vitamin D_3 analogues

Vitamin D_3 analogues (e.g. calcipotriol) inhibit T-cell activation, stimulate growth and differentiation of keratinocytes and melanocytes and induce melanogenesis by reducing the disturbed Ca^{2+} influx into melanocytes and restoring calcium homeostasis. Used as monotherapy in several studies, calcipotriol showed little or no treatment response [1] – combination with UVB was partially effective [10, 11, 12].

Table 1: Overview of studies.

Study (reference number)	Study type	Treatment mode (dose, frequency)	Patient number (age span)	Treated body areas	Treatment duration	Portion of patients with repigmentation (% of vitiligo areas)	Side effects/ remarks
4	RCT (pc, db, intraindividual comparison)	Syst. **PUVA; Calcipotriol** cream vs. placebo	35–29 usable	In addition to PUVA: one body half calcipotriol, other body half placebo		RP ≥ 75 % with - PUVA + calcipotriol: 63 % - PUVA: 15 % RP ≤ 25 % with - PUVA + calcipotriol: 81 % - PUVA: 7 %	Erythema, xerodermia, pruritus
5	RCT (pc, db)	**Syst. PUVA, Calcipotriol** cream vs. placebo	19		18 mo.	After 6 mo. (RP > 50 %): - PUVA+calcipotriol: 70 % - PUVA: 35 % After 18 mo. (RP > 50 %): - PUVA+ calcipotriol: 76 % - PUVA: 53 %	
7	RS	Syst. **PUVA** (cumulative dose in part over 1000 J/cm^2)	97 (26–50 y.)	Arbitrary	Observation over 10 y.	RP > 90%: 8.2 % RP 30–90 %: 60.8 % RP < 90 %: 28.9 %	Incomplete RP
3	CT	Syst. **PUVA** vs. cream **KUVA**	33 (6–59 y.) PUVA: 17 KUVA: 16	Not specified	1 mo.	PUVA: - RP > 60 %: 53 % - RP < 60 %: 47 % KUVA: - RP > 60 %: 43.8 % - RP < 60 %: 56.2 %	Syst. PUVA: 64.7 % erythema + pruritus, 52.9 % dizziness + vomiting, 35.3 % mild pain
6	CT	**PUVA** (topical)+ vs. **UVB-nb**	281	Arbitrary	PUVA 4 mo. treatment UVB 4 mo. treatment Further group: UVB 12 mo. treatment	PUVA (4 mo.) - RP > 75 %: 46 % UVB-nb (4 mo. - RP >75%: 67 % Further group: UVB (12 mo.): RP > 75 %: 63 %	Face: good RP Acral sites: poor RP
8	RCT (pc, intraindividual comparison)	**UVB** (nb vs. bb) vs. **Calcipotriol** cream (verum vs. placebo)	9 (35–51 y.)	**Right side of body:** calcipotriol **Left side of body:** placebo cream **Upper body:** UVB-nb **Lower body:** UVB-bb	12 mo.	After 6 Mon.: UVB-nb: 77.7 % show RP UVB-bb: no RP After 12 mo.: UVB-nb: - RP > 75 %: 22 % - RP < 75 %: 78 % UVB-bb: - RP > 75 %: 11 % - RP < 75 %: 89 %	UVB-nb: initial RP after an average of 11.8 wk. Calcipotriol: no improvement in terms of RP Questionable effect of multiple, parallel treatments

Table 1: Continued.

Study (reference number)	Study type	Treatment mode (dose, frequency)	Patient number (age span)	Treated body areas	Treatment duration	Portion of patients with repigmentation (% of vitiligo areas)	Side effects/ remarks
10	CT (pc)	UVB-nb; Calcipotriene ointment vs. placebo	17	In addition to UVB-nb: one body side calcipotriene, other side placebo		UVB + calcipotriene: - 52.9 % (n = 7) had significant improvement	
11	CT	UVB-nb	14 (12–56 y.)	Whole body	12 mo.	RP > 75 %: 71.4 % RP < 75 %: 28.6 %	28.6 % burning and pruritus, 21.4 % xerodermia
13	RCT (db)	Tacrolimus ointment (0.1% b.i.d.) vs. clobetasol propionate (0.05 % b.i.d.)	20 (< 18 y.)	Vitiligo sites on one side of body: tacrolimus Vitiligo sites on other side of body: clobetasol	2 mo.	Tacrolimus: - RP > 75 %: 25 % - no RP: 10 % Clobetasol: - RP > 75 %: 25 % - RP 51–75 %: 40 % - no RP: 10 %	90 % of all patients showed RP Tacrolimus: no side effects Clobetasol: skin atrophy in 15 % and telangiectasia in 10 % of patients
15	CT	Tacrolimus ointment (0.1 % b.i.d.)	19 verum and 15 control patients		24 wk.	89 % (17 pat.) showed RP RP > 75 %: 68 %	Minimal signs of irritation; vitiligo patients displayed significantly increased expression of IFN-γ, TNFα und IL-10 in affected and unaffected skin in comparison to controls.
16	RCT (intraindividual comparison)	Tacrolimus ointment (0.1 % b.i.d.) plus excimer laser (2 ×/wk.) vs. excimer laser monotherapy	14 (12–63 y.)	Intraindividual treatment with combined therapy and monotherapy as well as control sites	12 wk. (max. 24 treatments)	Tacrolimus + excimer: 100 % response RP > 75 %: 70 % Excimer monotherapy: 85 % response RP > 75 %: 20 %	Each treated area was compared to an untreated control area with all control areas showing no RP.
12	CT (intraindividual comparison)	Calcipotriol ointment	24 (5–59 y.)	Vitiligo sites in one side of body: calcipotriol Vitiligo sites on other side of body: untreated	Mean treatment duration: 3.9 mo. (3–6 mo.)	87.5 % (21 pat.) without repigmentation - RP 30 %: 1 pat. - RP 20 %: 1 pat. - RP 5 %: 1 pat.	The 2 pat. With 20 % and 30 % RP, respectively, showed 10–20 % RP in control lesions too.

Table 1: Continued.

Study (reference number)	Study type	Treatment mode (dose, frequency)	Patient number (age span)	Treated body areas	Treatment duration	Portion of patients with repigmentation (% of vitiligo areas)	Side effects/ remarks
14	CT	**Calcipotriol ointment vs. Clobetasol ointment** (each 2 ×/wk.)	42 Calcipotriol : 22 Clobetasol: 20		4 mo.	Calcipotriol: - RP 25–100 %: 18 % - RP < 25 %: 82 % Clobetasol: - RP 25–100 %: 65 % - RP < 25 %: 35 %	Calcipotriol: good tolerance, slight irritation and erythema Clobetasol: local erythema, acneiform papules and telangiectasia
20	CT (intraindividual comparison)	**Excimer laser vs. UVB-nb** (each 2 ×/wk.)	8 (29–58 y.), total of 23 treated areas	Left side: excimer laser Right side: UVB-nb	Max. 20 treatments (= 10 wk.)	Excimer laser: - RP 51–75 %: 17 % - RP 26–50 %: 30 % - RP ≤ 25 %: 26 % UVB-nb: - RP 26–50 %: 4 % - RP ≤ 25 %: 65 %	RP after 10 treatments with excimer laser significantly better than with UVB-nb ($p < 0.05$)
18	CT	**Excimer laser** (2 ×/wk.)	35 (52 treated areas)	Arbitrary	Max. 24 treatments	RP > 75 %: 26.9 %	
17	CT (uc)	**Excimer laser** (2 ×/wk.)	24 (11–58 y.)		9 mo. Mean number of treatments: 20	RP > 75 %: 29.2 % (7 pat.) RP 25–75 %: 25 % RP < 25 %: 25 % No RP: 20.8 %	Treatment effect stable after 12 mo.
22	CT	**TX** of cultivated autologous melanocytes after denudation with CO_2 laser	120	Arbitrary site; Comparison of stable localized, stable generalized and active generalized vitiligo		Stable localized vitiligo: - RP 90–100 %: 84 % Stable generalized vitiligo: - RP 90–100 %: 54 % Active generalized vitiligo: - RP 90–100 %: 14 %	
24	CT	**TX** of epidermis grafts after denudation of depigmented skin by erbium:YAG laser	21	Arbitrary	9–45 mo. follow-up	RP > 75 %: 71.4 % (15 pat.) RP 25–75 %: 9.5 % RP < 25 %: 19 % 1759.7 cm^2 repigmented skin surface of a total of 2315.8 cm^2 treated skin surface (75.9 %)	No scarring observed; stable RP during follow-up, no RP on upper extremities
23	CT	**TX** of melanocyte-keratinocyte grafts	142 (18–70 J.)	Various body sites	6 mo. follow-up	RP 95–100 %: 56% (80 pat.) RP 65–94 %: 11 % RP 25–64 %: 9 % RP 0–24 %: 24 %	

Table 1: Continued.

Study (reference number)	Study type	Treatment mode (dose, frequency)	Patient number (age span)	Treated body areas	Treatment duration	Portion of patients with repigmentation (% of vitiligo areas)	Side effects/ remarks
25	RS (uc)	Epidermis **TX** (suction blister epidermal grafting)	143	Comparison of generalized and segmental vitiligo	6 mo. follow-up	Generalized vitiligo RP 100 %: 53 % Segmental vitiligo RP 100 %: 91 % Pat. age < 20 y: RP 100 %: 82 % Pat. age > 20 y: RP 100 %: 58%	Hyperpigmentation: 32 % Infection: 6 %
26	RS (uc)	**L-phenylalanine** (oral: 50 or 100 mg/kg body weight; topical: 10 % gel) + 30 min. solar irradiation daily, subdivision into group with treatment in months with high UV irradiation and group with treatment in months of little UV irradiation	193	Arbitrary	6 y. treatment and visits every 6 mo.	RP 100 % (face): 84.1 % RP 100 % (trunk): 35.7 % RP 100% (extremities): 21.1 %	Significant difference in RP between both groups ($p < 0.05$)

Abbreviations: CT – clinical trial, RCT – randomized clinical trial, RS – retrospective study, uc – uncontrolled, b – blind, db – double-blind, pc – placebo-controlled, RP – repigmentation, TX – transplantation

Topical corticosteroids

Immunosuppressive therapy with highly potent topical corticosteroids (e.g. clobetasol) showed moderate treatment success in a comparative study with tacrolimus. Clobetasol was clearly superior to calcipotriol [13]. Well-known side effects of corticosteroids (especially cutaneous atrophy and capillary fragility) must be taken into consideration [1, 14].

Topical immunomodulators (TIM)

Macrolides such as tacrolimus and pimecrolimus act at the level of gene expression and suppress expression of proinflammatory cytokines (interleukins, TNFα and INFγ). Treatment with 0.1 % tacrolimus ointment over 24 weeks led to good repigmentation in 68 % [15]. Additional use of the excimer laser increases efficacy [16]. Treatment is tolerated well without side effects. The best results with TIMs could be achieved on the face and neck, where there is a potential risk for increased photocarcinogenesis [1]. Studies with high evidence levels are lacking.

Excimer laser

The excimer laser with a wavelength of 308 nm emits 200 Hz short microimpulses (60 ns) which accumulate on the treated skin area to a macroimpulse of the desired fluence. Each single impulse has a fluence of 3–4 mJ/cm^2. The fluence of the macroimpulse ranges from 50 to 350 mJ/cm^2. The limiting factor is the occurrence of erythema. The spot size is maximally 3.2 cm. In contrast to UV irradiation, targeted therapy of only the affected area with increased intensity is possible. In two studies the excimer laser achieved 30 % to 75 % good to very good responses (especially in the face) without causing side effects [17, 18, 19]. In comparison to UVB-nb, excimer laser achieved significantly better results after 10 treatment sessions [20]. In several studies excimer laser showed less success than topical corticosteroids and UVB-nb. Only with higher cumulative doses (50–73 J/cm^2) were good responses reported in several studies, with an increasing risk of UV-induced carcinogenesis. Repigmentation is also frequently inhomogeneous. The excimer laser can be recommended on the face in combination with topical immunomodulators.

Surgical therapy

In surgical procedures, melanocyte-containing specimens are grafted from healthy skin. These can be either directly cultivated melanocytes or specimens of epidermis [21]. The goal is direct

repigmentation. Good responses can be attained with all surgical procedures. One clinical study on the effects of grafting cultivated autologous melanocytes showed 90–100 % repigmentation in over 80 % of patients with stable localized vitiligo and in over 50 % of patients with stable generalized vitiligo [22]. Grafting melanocyte-keratinocyte suspensions in a further clinical trial resulted in 95–100 % repigmentation in over half of patients [23]. A small proportion of patients developed newly depigmented areas, partly in grafted skin. Transplantation of epidermal grafts resulted in good repigmentation in 70 % of patients, remaining stable for 9–45 months. On the upper extremities no repigmentation was achieved [24]. Using the technique of epidermal blister graft, where the superficial portion of a blister created by suction (suction blister graft) or by cryotherapy with liquid nitrogen is grafted from a normal into a depigmented area, 80 % or more repigmentation was achieved in several studies when treatment was combined with photochemotherapy [21]. A retrospective study (n = 117) on the suction blister graft showed significantly better responses in segmented that in generalized vitiligo [25]. With full-thickness punch grafting with epidermal biopsies (about 1.5–2.5 mm in diameter) transplanted from normally pigmented to depigmented areas, rapid and in a high percentage complete repigmentation can be achieved [21]. In grafting with cultured cells it was found that grafts containing keratinocytes along with melanocytes were superior to pure melanocyte grafts as melanocytes grew in a physiologic environment [21].

L-phenylalanine

L-phenylalanine is an inhibitor of cytotoxic antibodies and supports the stimulation of melanin synthesis and the migration of melanocytes from healthy into depigmented skin by solar irradiation. It is further a precursor in melanin synthesis. A retrospective study on 193 patients treated with L-phenylalanine showed very good results especially in the face [26]. Subjects who in addition to systemic L-phenylalanine (oral 50 and 100 mg/kg body weight) received high solar irradiation fared better than those who received less (30 minutes daily in each case). The optimal dose proved to be under 50 mg/kg daily. Repigmentation was poorest on the extremities.

Conclusions

On the basis of the presented data and the meta-analysis of Njoo et al. it can be concluded that in localized vitiligo UVB or PUVA therapy show the best results with the least side effects and are therefore treatments of first choice. In all 63 studies for localized and 117 studies for generalized vitiligo were considered and analyzed statistically [27].

Discussion

Vitiligo treatment encompasses various strategies depending on the form of vitiligo and the location of depigmented lesions with varying rates of success. Principally, results of any treatment are better on the face and neck, less so on the trunk and poorest on distal extremities. Phototherapy achieves good results especially in generalized vitiligo with UFB-nb appearing superior to UVB-bb. Vitamin D3 analogues such as calcipotriol do not show convincing results either as monotherapy or in combination treatment. TIM produce results similar to topical corticosteroids and are better tolerated, so they represent a reasonable option. Systemic corticosteroids will remain indispensable for rapidly progressive vitiligo.

Surgical techniques can be successful for small localized vitiligo. To prevent scarring and infection, such procedures should be performed by experienced

Table 2: Evidence levels.

Evidence level	Criteria/study type
1a	Systematic reviews (meta-analyses) of randomized controlled studies with high homogeneity
1b	Individual randomized controlled studies with narrow confidence intervals
1c	Randomized controlled studies, in which a disease was eradicated by a drug, or a disease, where formerly all patients died, is survived by some patients
2a	Systematic reviews of cohort studies with high homogeneity
2b	Individual cohort studies including randomized controlled studies of lesser quality (short follow-up, large confidence intervals)
2c	Studies with statistically significant differences between compared treatments
3a	Systematic reviews of case-control studies of high homogeneity
3b	Individual case-control studies
4	Cohort and case-control studies of poor quality
5	Expert opinion

(Sackett et al. 2000)

Table 3: Assignment of studies.

Evidence level	Studies
1a	27
1b	4, 17
2a	1, 8, 21, 28, 29, 30
2b	5, 10, 12, 13, 15, 16
2c	14, 20
4	2, 3, 6, 7, 9, 11, 18, 19, 22, 23, 24, 25, 26

physicians. That further limits the practicability of this treatment option. Therefore, they are not in routine use but serve as an important option for resistant, localized vitiligo. Photo (chemo)therapy is most effective in generalized vitiligo and UVB-nb is treatment of first choice for this vitiligo form. Combination with calcipotriol can improve results. Pure phototherapy is suitable to treat generalized vitiligo. Evidence exists that UVB irradiation is not associated with an increased risk of skin cancer, while it is definitely increased in PUVA therapy [28].

The excimer laser is a phototherapeutic alternative to conventional UVB therapy achieving good responses especially in localized vitiligo of the face; here the excimer laser may even be superior to UVB therapy. By combining with TIM, treatment response can be accelerated.

L-phenylalanine appears to achieve good results especially in the face, but is seldom used. Cosmetic techniques such as camouflage can be utilized. It should particularly be considered if the emotional burden is great – additional psychotherapy can also be helpful.

A representative evaluation of treatment forms is difficult, as available studies are largely case studies, pilot studies and clinical studies with only few patients and often poor control. Only few RCTs exist in the literature possessing adequately high levels of evidence. Therefore, the studies considered here are assigned to the respective levels of evidence in tabular form (Table 2, 3) [29].

Résumé

Table 3 shows that many of the included studies have low levels of evidence. For photo(chemo)therapy and treatment with TIMs, relatively many studies of high evidence exist; few studies exist for treatment with L-phenylalanine, but these have high evidence levels. One key problem of available studies is the low number of patients. Existing pilot studies and especially case reports can only suggest or show a tendency with respect to treatment response. In order to better evaluate vitiligo treatment methods, larger studies with longer follow-up and preferably randomized control groups should be performed. <<<

Conflicts of interest

None.

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