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Results of Combined Methods of Vitiligo Treatment – Emphasis on Multi-Wave Therapy

U. Yu. Sabirov, A. Sh. Inoyatov, Zh. R. Turdiev, U. Sh. Lutpullayeva

Republican Specialized Scientific and Practical Medical Center of Dermatovenerology and Cosmetology of the Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan

Abstract The treatment of vitiligo is still debatable. Numerous studies have been conducted around the world, in the CIS countries, and in our country on various aspects of vitiligo diagnosis and treatment, including the efficacy of various modes of vitiligo phototherapy using NB-UVB (311nm), excimer light (308nm), local use of immunosuppressants - tacrolimus, steroid hormones, liposomal drugs, antioxidants, PRP therapy, and systemic therapy with glucocortic. According to some authors, narrow-band NB-UVB therapy is the gold standard for the treatment of vitiligo. The mechanism of response to narrow-band therapy is two-fold: the first phase is pathological focus stabilization, the second is stimulation of melanocytes aimed at migration and melanogenesis, and cytokines act as a link, the synthesis of which is stimulated by UV irradiation. In the period from 2018 and 2022, 287 patients with non-segmental vitiligo (148 men and 139 women) aged 19-68 years applied to the State Institution "RSNPMTSDVIK". The average age was 28.1±1.3 years, the disease lasted 42.6±3.6 months, and 114 patients (40%) had vitiligo for less than a year before treatment. The study's purpose was to compare different methods of mono- and combined treatment of vitiligo, including a combination of different types of laser therapy. The treatment and concomitant autoimmune pathology, the phased first-line therapy of NB-UV in combination with Provitilin, followed by the connection of CO2 laser therapy, or the appointment of excimer light and its combination with an erbium laser, are the personifications of the approach in vitiligo.

Keywords Multi-wave therapy, Vitiligo, Combined treatment of vitiligo, Mono- treatment of vitiligo, Laser therapy

1. Introduction

The treatment of vitiligo is still a subject of debate. Numerous studies have been conducted in the world, in the CIS countries and in our country on various aspects of the diagnosis and treatment of vitiligo, the effectiveness of various modes of vitiligo phototherapy using NB-UVB (311nm), excimer light (308nm), local use of immunosuppressants – tacrolimus, steroid hormones, liposomal drugs, antioxidants, PRP therapy, as well as systemic therapy with glucocorticosteroids in the progression of the disease (van Geel N., 2020; Taieb A 2007-2022; Kanwar AG, 2013; Kubelis-Lopez DE, 2021) [1,2,7,9]. A number of authors consider narrow-band NB-UVB therapy to be the gold standard for the treatment of vitiligo [9]. The mechanism of response to narrow–band therapy is of a two–phase nature: the first phase is stabilization of the pathological focus, the second is stimulation of melanocytes aimed at their migration and melanogenesis, and cytokines act as a link, the synthesis of which is stimulated by irradiation in the UV range [5]. In particular, UVB rays stimulate the production of IL-1, IL-10, TNF-alpha, suppress local and systemic immune responses through the synthesis of pyrimidine dimers in the DNA of skin cells, isomerization of urocaninic acid, thus inhibiting lymphoproliferation [6]. One of the important effects of narrowband UV is considered to be stimulation of the release of regulators and inducers of melanogenesis - fibroblast growth factor and endothelin -1 from keratinocytes [5,8], as well as an increase in vitamin D metabolites due to the induction of synthesis of cholecalciferol from dihydrocholesterol in the skin [3]. The narrow-band UFO method is considered the safest and most effective, can be used for unstable vitiligo, has no contraindications in people with liver diseases, but there are drawbacks [8]. The method is contraindicated when taking certain medications (thiazide diuretics, tetracycline antibiotics, antidepressants), CVD, SLE, cutaneous porphyria, autoimmune bullous dermatosis. Of the side effects, the authors most often note itching, erythema, photoaging, xerosis, recurrence of herpes infection, carcinogenesis, because the absence of potentially active melanocytes increases the possible risk of malignant neoplasms of the skin. The positive effect of treatment is observed in 67% - 90% of cases, but it is difficult to achieve a complete cure of vitiligo. The popular expression: "Vitiligo is a dermatosis with infinite possibilities, but without any promises" describes the success of vitiligo therapy in the best

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possible way.

To increase the effectiveness of vitiligo treatment, researchers recommend various combinations of UFO therapy with local and general action of GCS, immunosuppressants, growth factor donors, as well as combinations of various types of laser therapy, the effectiveness of which varies widely and remains a subject for discussion. To select phototherapy modes, it is extremely important to identify the degree of disease progression, the reserve of repigmentation and localization of the process in view of the ambiguity of the response to phototherapy in various parts of the body. It is also important to take into account the quality of life of patients and their concomitant diseases, which can cause the trigger mechanism of depigmentation, or support it. The establishment of genetic factors is necessary to predict responsiveness to treatment, which may affect the tactics of therapeutic measures. All of the above dictates the need to continue scientific research in this direction.

The aim of the work was a comparative evaluation of various methods of mono- and combined treatment of vitiligo, including a combination of different types of laser therapy.

2. Materials and Methods

There were 287 patients with non-segmental vitiligo (148 men and 139 women) aged 19-68 years who applied to the State Institution "RSNPMTSDVIK" in the period from 2018 to 2022. The average age was 28.1±1.3 years, the duration of the disease was 42.6±3.6 months, while the onset of vitiligo for less than 1 year before treatment was in 114 patients (40%). All patients underwent a complete clinical and laboratory examination. The severity of the disease (prevalence, degree of depigmentation + quality of life) was assessed according to our proposed M-VES scale. In the M-VES scale, we propose to summarize the scores on 2 scales: VES [4] and DIKJ for a full assessment of the severity of vitiligo. PUVA, NB-UVB phototherapy was performed on the NEOLUX Series 3 unit (“Daavlin” USA), in the mode 3-5 times a week. Excimer light treatment was performed on an Excilite μ 308nm unit (DEKA, Italy). Laser irradiation was carried out by two types of lasers. A fractional Fr:CO2 laser with a wavelength of 10,600 nm was used, irradiation was carried out on a SmartXide installation with Punto technology (DEKA, Italy) in a fractional mode of 10W, 800 ms, 10600 nm. An erbium laser was also used. Laser irradiation with YAG:Er erbium laser was carried out at the Harmony XL Pro installation (Alma Lasers, Israel), in ablation mode, with a 9*9 mm nozzle, at a wavelength of 2940 nm, 1800 J/cm2.

3. Results and Discussion

We present the comparative results of the implementation of the proposed methods of combined treatment of vitiligo. Given the absence of a universal theory explaining the pathogenesis of vitiligo, in our opinion, it is justified to adhere to a personalized approach that takes into account the patient's condition, his physical and mental health, as well as the reserves of repigmentation, which are determined according to the non-invasive method of mexametry. Depending on the treatment, all patients were divided into 4 groups (Table 1).

The first group of patients received monophytotherapy (NB-UVB, either excimer light or PUVA). The second group of patients received monophototherapy (NB-UVB, or excimer light) in combination with the application of the cream "Provitilin". The third and fourth groups received multiwave combined phototherapy. In group 3, 2 combinations of NB-UVB with laser therapy were used: NB-UVB (311 nm) + CO2 laser (10600 nm) + Rulers, and NB-UVB (311 nm) + YAG: Er (2940 nm) + Provitilin. The fourth group was irradiated with excimer light (308 nm) in combination with lasers (YAG: Er 2940 nm, or CO2 laser 10600 nm) and "Provitilin" locally. With the progressive course of vitiligo, we followed the tactics of prescribing mini pulse therapy and NB-UVB locally or in the cabin. The course of mini pulse therapy included the appointment of GCS (dexamethasone) at a dose of 2-10mg per week for 2-6 months (Fig.1).

Table 1. Distribution of patients depending on the type of therapy

Type of phototherapy	The course of vitiligo	group 1, n	2 group n	3 group n	group 4, n	Total, n
NB-UVB	Unstable	50	35	16	21	122
	Stable	0	0	29	37	66
	Total	50	35	45	58	188
Эксимерный свет	Unstable	0	0	0	0	0
	Stable	19	24	16	18	77
	Total	19	24	16	18	77
PUVA	Unstable	0	0	0	0	0
	Stable	22	0	0	0	22
	Total	22	0	0	0	22
Total		91	59	61	76	287

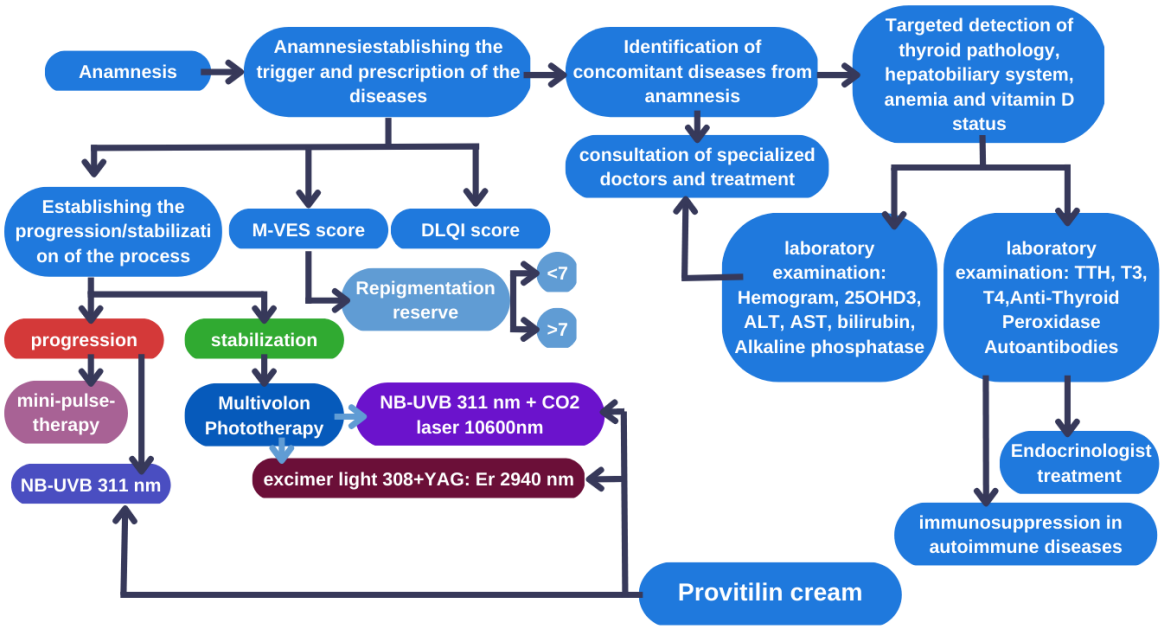

Figure 1. Algorithm for choosing treatment for vitiligo

Table 2. Results of combined methods of vitiligo treatment

Res-t	NB-UVB n=50		Excimer light n=19		NB-UVB+ Provitilin, n=35		Excimer light+ Provitilin, n=24		NB-UVB+Fr:CO2+Rulers n=45		NB-UVB+YAG:Er+Provitilin n=58		Excimer light +Fr:CO2+ About vitiligo, n=16		Excimer light+YAG:Er + Provitilin, n=18	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
great	17	34,0	10	52,6	18	51,4	12	50,0	33	73,3	34	58,6	12	75	15	83,3
good	16	32,0	7	36,8	8	22,9	10	41,7	5	11,1	13*	22,4	3	18,8	3	16,7
satisfying	11	22,0	2	10,5	7	20,0	2	8,3	7	15,6	8	13,8	1	6,2	0	0,0
unsatisfying	2	4,0	0	0,0	2	5,7	0	0,0	0	0,0	3*	5,2	0	0	0	0,0
-	4	6,0	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0	0	0	0	0,0
total	50	100	19	100	35	100	24	100	45	100	58	100	16	100	18	100

When evaluating the result of treatment, the regression of initial scores on the M-VES scale by 0-50% according to the Kawakami method, 2011 was taken into account: (regression of more than 50%M-VES) – excellent result, 25-50% - good, 10-25% - satisfactory, less than 10% - failures.); the sum of excellent and good treatment results it was considered a criterion for the success (effectiveness) of therapy.

The effectiveness of mono-phototherapy (group 1) was the best when using excimer light – 89.5%, with NB-UVB it was 66%, with PUVA - 72.7%. Poor treatment results were observed in 9.1% with PUVA, in 12% of cases with NB-UVB.

The addition of "Provitilin" (group 2) improved the results of monophototherapy from 72% to 81.4%, achieved complete stabilization of vitiligo in 100% of cases, and reduced the number of bad results from 9% to 3.4%, i.e. by 3 times. At the same time, the efficiency of excimer light in combination with "Provitilin" was significantly higher than NB-UVB, amounting to 91.7% versus 74.3% ($p<0.05$). Our results clearly demonstrate that the local effect of "Provitilin" containing trace elements and siliceous compounds, antioxidants, contributes to the effectiveness of phototherapy, possibly by affecting zinc- and selenium-containing enzymes SOD, heme-containing catalase, etc., and also creates an optimal microenvironment for the action of keratinocyte and fibroblast growth factors.

The effectiveness of multiwave therapy in the NB-UVB+Fr subgroup: CO2+Provitilin was 84.4%, and in the NB subgroup-UVB+YAG:Er+Provitilin – 81.0% ($p>0.05$), which indicates an equally high efficiency, however, with more excellent results in the subgroup NB-UVB+Fr: CO2+Provitilin: 73.3% vs. 58.6% in the NB-UVB+YAG subgroup:Er+Provitilin ($p<0.05$).

When combining excimer light of 308 nm and erbium laser YAG-Er 2940 nm, the number of excellent results was 83.3% versus 75% in the excimer light +Fr subgroup: CO2+Provitilin ($p<0.05$), overall efficacy in the Excimer light+YAG subgroup:Er+Provitilin was 100% versus 93.8% when using Excimer light+Fr:CO2+Provitilin ($p>0.05$) (Table 2).

Combined multi-wave phototherapy proved to be the most effective relative to monowave phototherapy, which allowed achieving excellent and good treatment results in 84.4% in the subgroup NB-UVB+Fr:CO2+Provitilin and 100% in the Excimer light+YAG subgroup:Er+Provitilin, and also allowed to establish the synergy of UFO and vitiligo laser therapy with the modulating effect of Provitilin.

The synergy of NB-UVB with CO2 laser and local application of Provitilin may consist in the fact that NB-UVB causes activation of melanocytes, and trace elements and antioxidants in the composition of Provitilin protect against excessive generation of ROS, activate SOD and catalase of the skin, and the biostimulating effect of CO2 laser provides a favorable cytokine and chemokine environment for activation melanogenesis and functioning of melanin-producing units (melanocytes and keratinocytes). The ablative effect of the CO2 laser ensures the death of damaged epidermal cells and damaged melanocytes, as well as melanocyte-cytotoxic CD8+ lymphocytes, freeing the "field of activity" from damaged cells for the proliferation and differentiation of normal keratinocytes, fibroblasts, melanocytes. Ablation under the action of a CO2 laser occurs when water is instantly heated above 100℃ and tissue evaporation occurs. This effect improves the structure of the epidermis and pigmentation, coagulation zones outside the ablation zones, where temperatures occur, cause collagen denaturation (65-67℃) and subsequent remodeling. At the same time, with impaired cytokine and chemokine regulation, as well as impaired regulation of apoptosis due to mutation of REL, TNFAIP3 genes, these effects are poorly expressed, which caused resistance to treatment in such patients in our work.

Based on our own results, we propose a hypothesis according to which lasers (CO2, eribium) provide ablation and photothermolysis with the formation of a microthermal treatment zone - channels for the penetration of both drugs (Provitilin) and mediators and chemokines – regulators of cell division and apoptosis deep into the skin, as well as their migration into the epidermis, where and their effects are realized at the level of melanocytes and keratinocytes. Due to photothermolysis, some of the damaged cells die, freeing up space for the development of healthy ones, which, in a favorable environment with an optimal amount of trace elements, antioxidants, can provide melanogenesis and skin repigmentation. The biostimulating effect of UV and excimer light is enhanced, their immunosuppressive and immunomodulatory effects are realized in the skin. To confirm our hypothesis, further morphological and immunohistochemical studies are needed. At the same time, we found that with the carrier of unfavorable alleles of the REL, TNFAIP3 genes, the effectiveness of phototherapy is low, which may be due to a shortage of products of these genes involved in pro-inflammatory and anti-apoptotic cascades.

Thus, with multi-wave therapy, the effect is realized both in the deep layers of the skin and at the level of the epidermis, manifested by photothermolysis, biomodulation, changes in the physico-chemical properties of the tissue, and Provitilin, due to its balanced composition, provides a protective effect from the side effects of lasers and creates a favorable microenvironment for the effects of growth factors released during stimulation phototherapy.

In our opinion, one of the significant results of the work is the synergism of multiwave therapy that we have identified, when the best result was with a combination of radiation in the range of 311 nm and 10600 nm (NB-UBV + CO2 laser), as well as with radiation of 308 nm and 2940 nm (excimer light + erbium laser). In general, out of 287 patients, 161 (56.1%) had excellent results, 71 (24.7%) had good results, 42 (14.6%) had satisfactory results, 9 (3.1%) had unsatisfactory results, and 4 (1.4%) had progression.

4. Conclusions

1. The overall effectiveness of monophototherapy was the best when using excimer light – 89.5%, with NB-UVB it was 66%, with PUVA - 72.7%. Poor treatment results were noted in 9.1% of cases with PUVA, in 12% of cases with NB-UV, in general, the effectiveness of monophototherapy was 72%. The addition of Provitilin made it possible to improve the results of monophototherapy from 72% to 81.4%, achieve complete stabilization of vitiligo in 100% of cases, and reduce the number of bad results from 9% to 3.4%, i.e. by 3 times. At the same time, the effectiveness of excimer light was significantly greater than NB-UV-B ($P<0.05$), amounting to 91.7% with combined Provitilin therapy, versus 74.3% for NB-UVB rays.
2. Multi-wave effectiveness of therapy in the subgroup of NB-UV - +fr:CO2+Provitilin was 84.4%, and in the NB subgroup-UV+laser:RP+Provitilin – 81.0% ($P>0.05$), however, with more excellent results in the subgroup NB-UV - +fr:CO2+Provitilin: 73.3% vs. 58.6% in the NB-UV+laser subgroup:RP+Provitilin.
3. When combining excimer light of 308 nm and erbium laser YAG-RP 2940 nm, the number of excellent results was 83.3% versus 75% in the Excimer light +fr subgroup:CO2+Provitilin ($P<0.05$), total efficiency in the Excimer light+laser subgroup: RP+Provitilin was 100% versus 93.8% when using Excimer light+fr:CO2+Provitilin.
4. Combination therapy multi-wave phototherapy was the most effective, which allowed to achieve excellent and good treatment results in 84.4% in the subgroup of NB-UV - +fr:CO2+Provitilin and 100% in the Excimer light+Laser subgroup:RP+Provitilin ($P<0.05$), which indicates the synergy of UFO and vitiligo laser therapy with the modulating effect of Provitilin.
5. A comparative evaluation of the results of combined phototherapy with multiwave allowed us to establish synergy, when the best result was with a combination

of radiation in the range of 311 nm and 10600 nm (NB-UBV + CO2 laser), as well as with radiation of 308 nm and 2940 nm (excimer light + erbium laser) in combination with Provitilin, modulating and having a protective effect.

6. The personification of the approach in vitiligo consists in the treatment and concomitant autoimmune pathology, the phased first-line therapy of NB-UV in combination with Provitilin, followed by the connection of CO2 laser therapy, or the appointment of excimer light and its combination with an erbium laser.

REFERENCES

[1] Vaisov A.S. The role of hormonal imbalance in the pathogenesis and treatment of vitiligo, the development of a complex method of photochemotherapy in a hot climate. diss. Doctor of Medical Sciences. - M., 1989. — 36 p.

[2] Vladimirov V.V. Skin and venereal diseases: Atlas. - 2016. -Moscow: GEOTAR-Media. -226 p .

[3] Talnikova E.E. Vitiligo: modern methods of therapy (review) // Saratov Scientific Medical Journal. 2017. Vol. 13, 3 no. -pp. 668-673.

[4] Inoyatov A.Sh , Khodjaeva N.B., Sadiev S., Narziev J. New approaches to the diagnosis of vitiligo // "American Journal of Medicine and Medical Sciences. - 2022.- 12(12): 1309-1318 // DOI: 10.5923/j.ajmms.20221212.27.

[5] Fitzpatrick tuberculosis. Mechanisms of vitiligo phototherapy // Arch Dermatol 1997; 133:1591-2.

[6] Frizoli M. L., Essien K., Harris J. Vitiligo: mechanisms of pathogenesis and treatment // Annual report Immunol. 2020 April 26;38:621-648

[7] Gomez I.A., F.O. de Carvalho, A.F. de Menezes, F.M. Almeida, S. Shanmugam, J. de Souza Siqueira Quintans, L.J. Quintans-Junior, T.R. de Moura, P.D. Oliveira, A.A. de Souza Araujo. The role of interleukins in vitiligo: a systematic review // Journal of the European Academy of Dermatology and Venereology. -2018.- Volume 32, issue 12.

[8] Westerhof V., Nieuweboer-Krobotova L. Treatment of vitiligo UV-B against local psoralen plus UV-A // Arch. Dermatol. -1997; 133:1525-8.

[9] Gil wang N, Hamzawi I, Kohli I, Volkerstorfer A, Lim Hu, Bei JM, Louis H, Harris J, Pandya AG, Thong Tian Guan S, Abdallah M, Esmat S, Seneschal J, Spikert R, L Green, Kang Hee, Rabubi N, Xiang L.F., Beckenk M., Picardo M., Tayeb A. Standardization of serial photography for the assessment and monitoring of vitiligo: a basic set of international recommendations on basic clinical and technical characteristics // J.Am acad Dermatol. 2020 December; 83(6): 1639-1646.