Multicenter study of the efficacy on combination therapy on patients with vitiligo (narrowband phototherapy in combination with VITISKIN local antioxidant)

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SUMMARY

The aim of the study was to assess the effectiveness of combination therapy (light therapy by narrow-band UV-B (UVB TL01) with a wavelength of 311 nm plus topical treatment with Vitiskin) and monotherapy of vitiligo with Vitiskin gel compared to control with Neutral gel instead of Vitiskin.

Materials and methods. For the study 72 patients with vitiligo were randomly selected and divided into three groups of 24 people. Group 1 applied the gel only for the first 4 weeks, then combined it with 311 nm UVB for the following 10 weeks. Group 2 received topical gel in combination with UVB therapy for 10 weeks. Group 3 was treated with the gel without UVB therapy for 14 weeks.

Results and discussion. Topical application of Vitiskin gel, both as monotherapy and in combination with 311 nm UVB therapy, has a positive effect in terms of perifollicular and peripheral repigmentation of vitiligo patients compared with the application of the control neutral gel.
Combination therapy (topical Vitiskin gel and narrow-band 311 nm UVB) gives good short-term results in the treatment of vitiligo. The best effect is produced by the concurrent therapy (Vitiskin gel plus UVB), but the best tolerability of treatment was shown in Group I (at first local antioxidant Vitiskin gel for 4 weeks, followed by 10-weeks' gel combination with 311 nm UVB).

Conclusions. Application of Vitiskin gel as topical therapy in combination with 311nm UVB provides significant benefits to vitiligo patients.

Key words: vitiligo, Vitiskin gel, UVB 311 nm.

INTRODUCTION

Vitiligo is an acquired condition that causes partial or generalized depigmentation of the skin. It affects 0.5% of the population in all age groups[1, 2] without distinction as to race or gender. Etiopathogenetic mechanisms of the disease are still not sufficiently clear and that makes it not always possible to stop the progress of dermatosis even during therapy. Vitiligo vulgaris is an acquired chronic disorder of pigmentation, which appears as depigmented white patches, often symmetrical, usually increasing in size with time. Vitiligo is associated with a significant loss of function of epidermal melanocytes and sometimes the melanocytes of hair follicles[1,2,3]. Several studies have shown that it is common to all groups of patients with vitiligo to have increased lipid peroxidation, which leads to accumulation of lipid hydroperoxides, conjugated dienes and malondialdehyde levels in blood. The changes in enzymes of the antioxidant system, controlling the level of reactive oxygen species, were also detected. Patients with vitiligo also show a decrease in activity of superoxide dismutase and catalase. Several authors confirm the decrease in the activity of exogenous enzymes in various pathological processes[2,3,4]. In this regard, the study of pathogenic mechanisms of depigmentation and search for appropriate therapeutic measures for patients with vitiligo is one of the important directions of modern dermatology.

In evaluating a patient with vitiligo the important factors are the patient's age, concomitant diseases, (especially autoimmune disorders), prior treatment and the extent, stage and activity of vitiligo, as well as the psychological condition of the patient[4,5,6]. Once these factors are taken into account, a clinician can proceed to draw a plan of examination and treatment. Since the management of patients with vitiligo often takes a long period of time, patients are sometimes frustrated by the effectiveness of previous treatment. In such cases, they suffer from psychological stress, and such patients need support and consultation by a psychotherapist. The treatment plan should be discussed with the patient to ensure an adequate level of compliance. Prior to starting vitiligo therapy, autoimmune disorders, especially thyroid disease (including autoimmune polyglandular syndrome), shall be ruled out.

In recent years, one of the pathogenetic treatment methods has been the application of topical antioxidants and UVB therapy (UVB TL01) with a wave length of 311 nm[4,7,8]. Vitiskin Gel was developed against depigmentation; it contains as one of its ingredients superoxide dismutase, contributing to neutralize free radicals, whereby stimulating overall metabolism in cells[4,7]. Vitiskin is a hydrogel applicable at all levels of management of depigmentation.

The mechanism of therapeutic action of this topical medication helps to balance the cellular metabolism with antioxidants. Vitiskin includes components of superoxide dismutase, copper, zinc, vitamin B12 and calcium pantothenate (a precursor of melanin). Superoxide dismutase, a quick-acting and the most stable enzyme whose concentration in Vitiskin is high, eliminates the chain of free radicals, possesses anti-inflammatory properties, retards lipid peroxidation, thereby increasing the effectiveness of therapy. Copper and zinc help protect against oxidative damage. Vitamin B12 is involved in the synthesis of melanin and is indispensable in the metabolism. Calcium pantothenate also participates in the melanin synthesis and is necessary for the copper absorption. External therapy by a topical gel with superoxide dismutase and catalase activity, active at all stages of depigmentation regulatory process, may be more effective when used in patients with vitiligo in combination with narrow-band medium wave radiation with a wavelength of 311 nm.

The aim of the study was to assess the effectiveness of combination therapy (light therapy by narrow-band UV-B (UVB TL01) with a wavelength of 311 nm plus topical treatment with Vitiskin) and monotherapy of vitiligo with Vitiskin gel compared to control (Neutral gel instead of Vitiskin.)

MATERIALS AND METHODS

For the study, 72 patients with vitiligo were randomized and divided at random into three groups of 24 people each. The study design is presented in Table 1. Criteria for inclusion in the group were: age ≥ 18 years old, generalized or localized form of the disease, two symmetrical areas of depigmentation (except for the face), the patient not involved in other clinical trials. In two groups patients gave their written informed consent for selective treatment by UVB (311 nm). Exclusion criteria were: pregnant or breastfeeding women, allergic rash in response to solar radiation, patients with dermatitis, acute or chronic somatic diseases, history of any local or systemic treatment of vitiligo in the last 4 weeks prior to the study, allergic reactions to Vitiskin or any of its ingredients.

Table 1. Vitiligo treatment duration and pattern

GROUP 1 (partial combination)	4 weeks	10 weeks
	Vitiskin gel/ neutral gel	Vitiskin gel/neutral gel plus UVB 311 nm
GROUP 2 (full combination)	10 weeks	
	Vitiskin gel/neutral gel plus UVB 311 nm	
GROUP 3 (mono therapy)	14 weeks	
	Vitiskin gel/ neutral gel	

Depending on the group, for 10 or 14 weeks, Vitiskin gel was applied twice a day to depigmentation and surrounding areas on one side, and on the other side the neutral gel was applied. Patients in group 1 (partial combination) applied Vitiskin gel and the neutral gel twice a day for 4 weeks and then for further 10 weeks continued topical therapy in combination with narrow band 311 nm UVB, three times per week (total number of treatments - 30).

Group 2 (full combination) applied Vitiskin and the neutral gel on symmetrical zones simultaneously in combination with UVB therapy (311 nm) three times a week from Day 1. The initial dose of UVB therapy was 0.07 J/cm^2 and was increased each session by 0.01 J/cm^2 to obtain erythema and reach a plateau.

Group 3 (monotherapy without UVB) received only topical treatment with Vitiskin gel and neutral gel without UVB therapy for 14 weeks.

Evaluation of the study results was carried out according to VIMAN clinical index (which was calculated separately for symmetrical areas and as a general index of all lesions of the skin). Severity (mild, moderate, severe), changes in depigmentation areas[9], and tolerability were also assessed. The methods used were macrophotography, self-assessment and patient questionnaires. When calculating scores of VIMAN index, the tendency to perifollicular and peripheral repigmentation during therapy was taken into account.

Treatment efficacy was assessed on a 6-point scale (deterioration, no change, slight improvement, improvement, significant improvement, clinical remission), where «deterioration» means negative trend in the skin process in comparison with the initial condition; «no change» means –no changes in skin process in comparison with the initial condition; «slight improvement»: –repigmentation of the skin area less than 15% from baseline; «improvement»: –repigmentation from 15% to 50% of the skin compared with the original data; «significant improvement»: –repigmentation from 51% to 95% of the skin compared with the original data; «clinical remission»: –repigmentation from 96% to 100% of the affected skin areas.

Progression of vitiligo areas was assessed on a 7-point scale as follows: no change, mild diffuse repigmentation, light uniform repigmentation, average diffuse repigmentation, uniform average repigmentation; almost complete repigmentation, not fully covering the affected area; complete recovery of the pigment.

Tolerability of Vitiskin was evaluated according to the criteria of erythema, dryness, exfoliation, itching, burning, tingling on 0-to-4-point scale: no side effects - 0; little effect - 1; moderate effect - 2; moderately severe - 3; severe - 4. Before and after therapy the affected areas were photographed to assess the condition of the skin at different points in time under the same conditions. Evaluation of the cosmetic properties of the Vitiskin gel and neutral gel (texture, ease of application, time of soaking and scent) was made by patients themselves during the last session.

RESULTS AND DISCUSSION

Clinical history and clinical characteristics of patients with vitiligo are shown in Table 2. Thirty patients (41.7%) suffered from the disease from childhood or adolescence. Positive family history of vitiligo was found in 35 (48.6%) patients. Fitzpatrick skin type II was observed in 59.7% of the patients. According to 36 (50%) patients, stress was a precipitating factor of the disease, and in 21 (29.2%) patients the cause of the dermatosis was not specified. The average severity of the disease (from 301 to 800 points) was observed in 45 (62.5%) patients. Generalized form prevailed in 56 (77.8%) patients. Colors of affected areas ranged from milky white to lime white and ivory, rarely - of porcelain colour. For topical therapy the following symmetrical lesions were selected: shoulders – in 4 patients, forearm – in 21, hands – in 10, hips - in 8, shins – in 10, feet – in 9, and abdomen - in 5 patients.

In assessing the overall efficiency after therapy it was stated that the therapeutic effect (significant improvement and improvement) occurred on the tested (right) side with Vitiskin gel in 52 (72.2%) patients as compared to the use of the neutral gel on a symmetrical area in 21 (29. 2%) patients (Fig. 1).

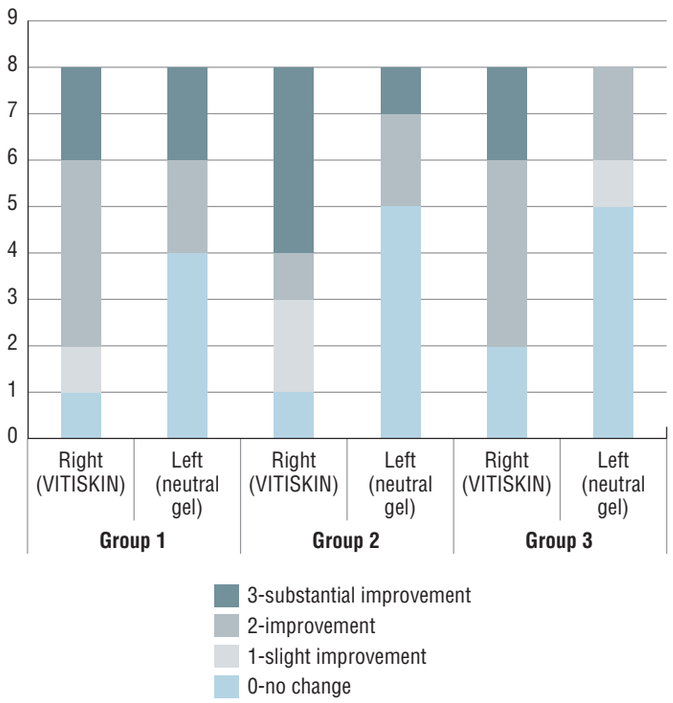
No effect at all was produced on the left side of the symmetrical affected area (neutral gel) in 34 (47.2%) patients, incl. 8 (33.3%) patients in Group 1 and in Group 2 and 18 (75%) patients in Group 3, respectively.

Table 2. Vitiligo patients' history and clinical records

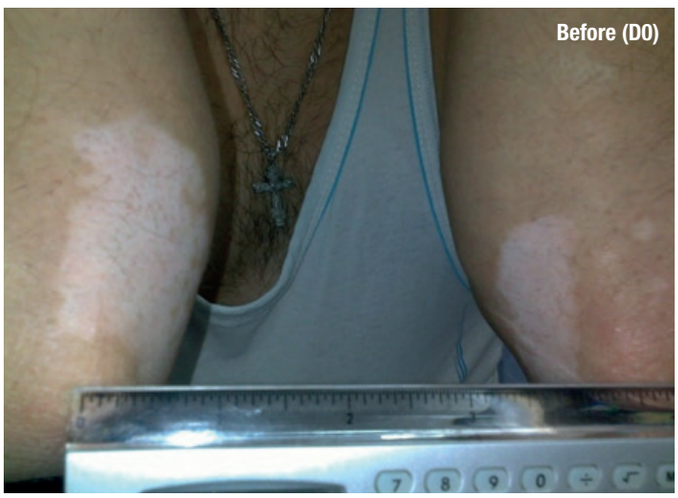
History and clinical records	Number of patients (%) n = 72
Sex	
Male	38 (52.8%)
Female	34 (47.2%)
Age at onset of disease	
Up to 16 years old	30 (41.7%)
Over 16 years old	42 (58.3%)
Duration of disease in years	
Below 4 years	11 (15.3%)
5-10	15 (20.8%)
11-15	22 (30.5%)
16-20	16 (22.2%)
Over 20 years	8 (11.1%)
Inheritance (family history of vitiligo)	
Yes	35 (48.6%)
No	37 (51.4%)
Fitzpatrick skin type	
I	3 (4.2%)
II	42 (59.7%)
III	24 (33.3%)
IV	2 (2.8%)
Initiating agent	
Stress	36 (50%)
Infections	4 (5.6%)
Intensive exposure to sunlight	11 (15.3%)
Pregnancy	2 (2.8%)
Cause unknown	21 (29.2%)
Clinical forms	
Generalised	56 (77.8%)
Localized	16 (22.2%)
Severity (VIMAN index)	
Light	13 (18.1%)
Moderately severe	45 (62.5%)
Severe	14 (19.4%)

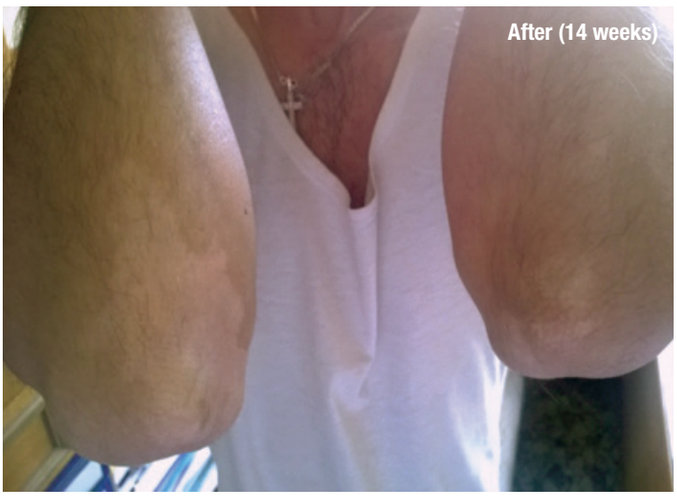
These findings are supported by a comparative analysis of average total VIMAN index in the affected area on the active side in each of the groups: Group 1 - before treatment the index was 37.5 points, after treatment - 23.63 points (positive dynamics was 58.73%); Group 2 - before treatment - 37.5 points, after - 24.75 points (an improvement of 51.52%); Group 3 - before treatment - 33.75 points, after - 21.38 points (dynamics of index improvement was 57.89%). Fig. 2a and 2b show clinical results of the treatment in a patient from Group 1 (partial combination), which started with topical therapy for 4 weeks, followed by additional 10 weeks' UVB (UVB TL01).

Figure 1. Overall comparative clinical effectiveness of treatment methods using Vitiskin gel and neutral gel in 3 groups



Figures 2a (before treatment) and **2b** (after treatment). Result of treatment of a patient in Group 1 (partial combination); right - Vitiskin gel and UVB; left - neutral gel and UVB.

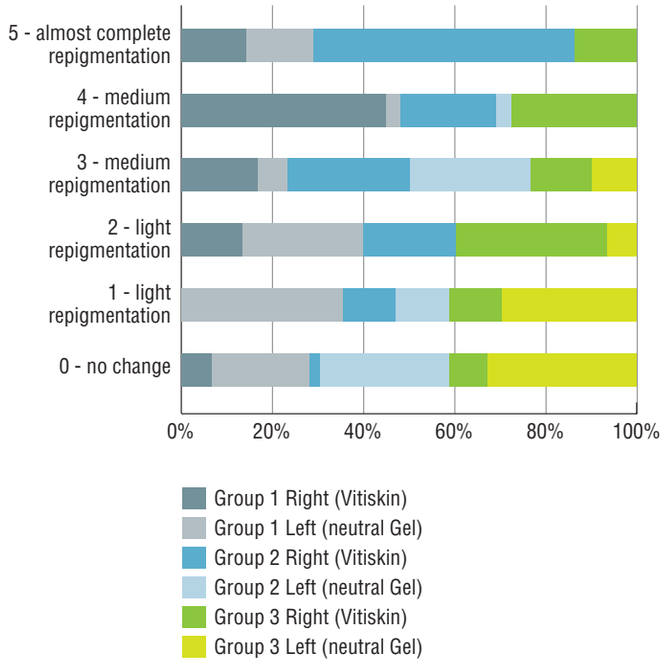




According to repigmentation assessment after therapy in all groups

the active right side showed either mild or moderate uniform and diffuse repigmentation (Fig. 3). On the control side (neutral gel) in 38 (52.8%) patients no repigmentation occurred. Figures 4a & 4b show repigmentation in a patient after combination therapy (UVB and simultaneous topical application of Vitiskin) for 10 weeks (Fig. 4a and 4b). However, when evaluating peripheral and/or perifollicular repigmentation on the active side it was revealed that the positive results were almost identical in all three groups compared to the control side (Fig. 5). Nevertheless, when using the total VIMAN index (based on the whole surface of affected areas before and after treatment) statistically different data were obtained on therapeutic efficacy in the three groups of patients.

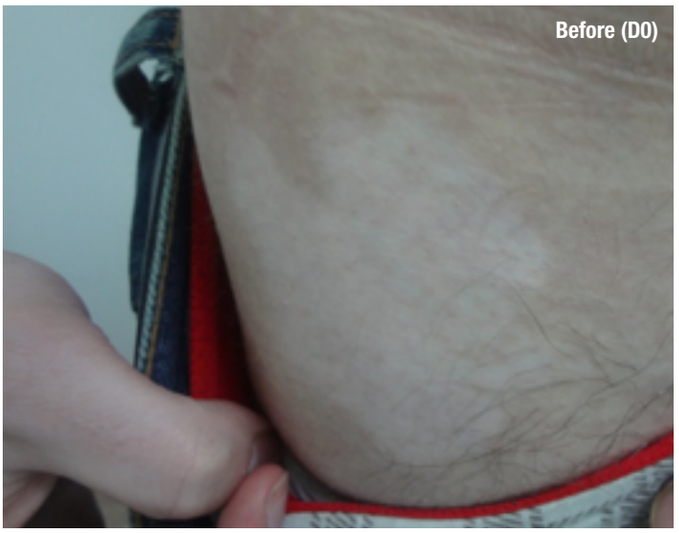
Figure 3. Comparative analysis of vitiligo areas repigmentation in 3 Groups with symmetrical application of Vitiskin gel and neutral gel.

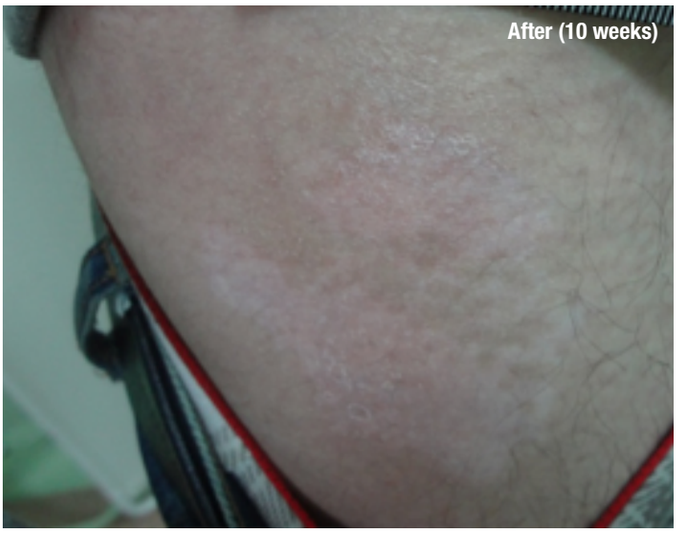


Group 2 showed the most evident and significant improvement of the clinical index averages (before treatment - 543 points, after treatment - 459 points, which makes up 15.43% improvement in the dynamics of the results). In Group 1 the dynamics of the results showed the following: before treatment - 596 points, after - 557 points (6.52% improvement in the index). In Group 3 the index before treatment was 345 points, and after therapy - 329 points (4.53% positive dynamics of the index).

The most effective therapy was observed in vitiligo spots located on the skin of the chest and thigh: up to 90% respectively. A much lower effect, regardless of the chosen method, was observed in depigmentation spots on the feet, where repigmentation did not exceed 20%. It was noted that the occurrence and extent of repigmentation depended on the disease duration, since most actively repigmented were the areas which had been affected for 1 to 4 years. Narrow-band phototherapy was more effective in cases of vitiligo vulgaris and acral vitiligo. It should be noted that after therapy repigmented spots in vitiligo areas had normal color of the surrounding skin and the skin did not look patchy due to various color shades that are often observed in such patients after combination of long-wave ultraviolet rays and photosensitizers (PUVA therapy).

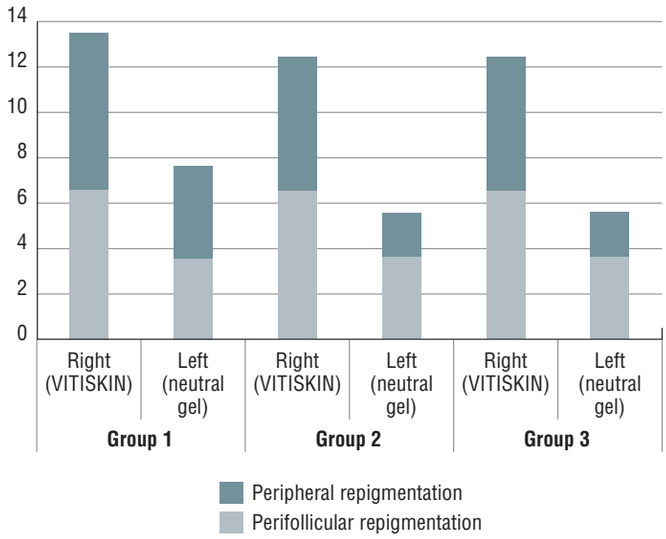
Figures 4a (before treatment) and **4b** (after treatment). Diffuse repigmentation in vitiligo patients who received the full combination therapy for 10 weeks.





Treatment was well tolerated by most patients. Adverse effects were observed on the top of already administered therapy only in groups with UVB. Most often, patients complained about erythema (13.9%) and dry skin (13.9%): in Group I – 5 patients (6.9%) and in Group II – 6 (8.3%) respectively. The side effect of burning (8.3%) after 1-2 min of application of the active medication was registered in Groups I and II – in 2 patients (2.8%) respectively, in Group III – in 3 (4.2%); the effect of itching (8.3%): in Groups I and II – in 2 patients (2.8%) respectively, in Group III – in 3 (4.2%), and exfoliation of the skin (8.3%) was seen in Group I and II – in 2 patients (2.8%) respectively. Adverse effects subsided rapidly after dose reduction or short-term cessation of UVB therapy and did not require any administration of medicines or withdrawal from the study. All patients appreciated the texture and ease of application of the gel. Pleasant or neutral odour of the gel was noted by 61 (84.7%) patients. Quick time (5 minutes) of the gel absorption was pointed out by 67 (93%) patients. Combination topical therapy with Vitiskin gel and UVB TL01 therapy resulted in earlier skin repigmentation in vitiligo areas on the side where the active substance was applied. The control side where the neutral gel was applied for comparison showed no well-evident positive changes. The effect of combination therapy on vitiligo patients was probably due to simultaneous application of the topical gel with superoxide dismutase and catalase activity, acting at all stages of repigmentation process, and the mechanism of action of narrow-band medium wave radiation (wavelength of 311 nm). It should also be noted that the results of therapy depend on the localization of vitiligo areas and duration of the disease, which emphasizes the need for earlier diagnostics and treatment of patients with this pathology.

Figure 5. Peripheral and perifollicular repigmentation before and after therapy in symmetrical areas (right and left).



The purpose of topical therapy of vitiligo patients is to achieve clinical recovery or significant improvement of the skin process. The results of treatment showed that the combination of the dermatic – Vitiskin gel and narrow-band medium wave radiation, wavelength 311 nm (UVB TL01) is more effective than monotherapy by Vitiskin gel for 14 weeks, and more effective than 4-week monotherapy by Vitiskin gel followed by UVB TL01 treatment for 10 weeks.

CONCLUSIONS

Topical application of Vitiskin gel both as monotherapy and in combination with 311 nm narrow-band UVB therapy has a positive effect leading to perifollicular and peripheral repigmentation of vitiligo lesions compared with control application of the neutral gel.

Combination therapy (topical Vitiskin gel and narrow-band 311 nm UVB) gives good therapeutic results (significant improvement and improvement) in patients when compared to the use of the neutral gel on the symmetrical side.

The best effect is produced in case of concurrent therapy with Vitiskin gel and UVB TL01 (311nm) in comparison with the hydrogel monotherapy. The results of the study also confirm good tolerability of Vitiskin gel.

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