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## Vitiligo Treatment Algorithm.

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### Abstract

The strategy of managing patients suffering from vitiligo is described, including focusing of patient's motivation to long-term treatment and informing patients to exclude false expectations as a reason for a lack of satisfaction and premature termination of treatment. Provided algorithm of vitiligo treatment, besides general recommendations and prescriptions, contains five steps, which are applied sequentially when a preceding one lacks efficiency or maximally achievable effect is reached. Application of the algorithm allows for reaching pronounced repigmentation of vitiligo lesions in 80-90% of cases and assuring long-term, often lifetime, remission of vitiligo.

**Keywords:** melanocytes, vitiligo, treatment algorithm.

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## INTRODUCTION

Vitiligo is associated with a disorder of melanocytes. Melanocytes are sensitive cells, they transform external and internal signals into a regulatory system that establishes homeostasis in the skin. The unique properties of melanocytes are associated with the production of neurotransmitters, neuropeptides, the production of which is stimulated by UV and agents within the neuroendocrine system of the skin. Evidence of neuroendocrine activity of melanocytes is the production of DOPA, its metabolites and catecholamines [1].

Some researchers have found the ability of melanocytes to transform L – tryptophan into serotonin and melatonin. Melanocytes produce corticotropin-releasing factor (CRF) and urocortin and express appropriate CRF receptors [2]. Also, melanocytes synthesize proopiomelanocortin (POMC), which is a precursor of hormones: lipotropin, ACTH, endorphins [3]. Melanocytes can express elements of the hypothalamic-pituitary system and cholinergic system [4]. Regulation of melanogenesis is associated with the action of: melanocyte stimulating hormone, stem cell factor (SCF), endothelin -1, nitric oxide, ACTH, prostaglandin, histamine [5].

Today, a number of vitiligo pathomechanism theories exist including genetic, autoimmune (or immune), oxidative stress (biochemical infringements), neurogenic (neuroendocrine), melanocytotoxic (autodestruction), convergent theories, etc. Each of the above theories has scientifically sustainable data both supporting and disproving it. Also, it should be noted that the segregation of these theories is rather relative as there are clear direct and indirect interconnections between unexceptionally all processes that - as it is currently considered - result in vitiligo development. Moreover, all they are constituents of a complex of biochemical reactions and cellular interactions which can not be considered separately.

The lack of a single consensus theory of vitiligo etiology and presence of multifactorial genetic predisposition to vitiligo results in absence of radical remedies for a cure. Vitiligo treatment is a relatively complex process but nonetheless, a number of methods currently exists which allows for reaching acceptable results.

**To treat or not to treat?** In our opinion, the first thing a dermatologist should do when seeing naive vitiligo patients (if a patient has already been diagnosed with vitiligo) or diagnosing with this condition, is to evaluate the patient's psychological attitude to the disease (quality of life), as their attitude is directly linked to motivation for treatment.

As vitiligo does not cause any physical malfunction or discomfort and does not affect lifespan, we think that a necessity of treatment should be justified by a patient after giving him comprehensive information about essence of the disease and available therapeutic interventions (on one hand, the physician should not say that vitiligo is untreatable; on the other hand, dermatologist should not "frighten" a patient and to force him to treatment). In our practice, we envision many patients who solely want to confirm their diagnosis. Such type of patients includes young men of military calling age to get an exempt from military service duty, persons undergoing routine periodical medical examination, persons willing to confirm their diagnosis of vitiligo and to assure lack of danger from the disease. Such patients are quite satisfied with their skin condition and have no willingness to go through lengthy treatment course, which requires constant attention (for example, regular application of topical drugs, attendance of phototherapy sessions, etc.). In our opinion, enforcement for getting treatment for such patients is not necessary. Similarly, it applies to adolescents if parents are not inclined to medical treatment of a child in case the vitiligo is not a concern for a child. In this case, there is no need to offer a treatment from the point of view of social adaptation. Such patients require psychological calming, recommendation to use photoprotectives when under the sun exposure, and, if necessary and desired, to use cosmetic camouflage.

In case of a strong motivation for a treatment of vitiligo (usually this is related to strong impairment of life quality), a patient should be informed about possibility of treatment success but also warned that a treatment will be lengthy and multi-staged.

**Before treatment.** Prior to prescription of a particular treatment, dermatologist should obtain certain information from a patient such as details about his/her regional specific, co-morbid diseases (especially those

of autoimmune nature), and, if required, to send a patient for laboratory test and consultations of relevant specialists.

General and conventional schemes of primary examination of vitiligo patients do not exist. Therefore, usually it is not necessary to prescribe numerous laboratory tests and examinations by other specialist, some of which are expensive and might be unavailable for a particular patient.

Nonetheless, when dealing with generalized form of vitiligo, it is feasible to obtain the opinion of an endocrinologist on the thyroid state (usually consultation includes ultrasound examination and blood tests for thyroid hormones). It is advisable to explain to a patient that thyroid disease might "support" or "provoke" vitiligo due to similar pathogenesis, and the same relates to other autoimmune diseases. If a malfunction of the digestive tract are noticed, or a patient lives in countryside, especially in Middle Asian region, it is desirable to test for helminthes, which although not frequently, might facilitate vitiligo development. Despite the presence of melanocytes in inner ear, pigmented part of the retina and vascular layer of eye, we suppose that examination of hearing and visual functions are not informative as we lack convincing evidences on hearing loss or visual function decline as co-morbid vitiligo conditions.

In our practice, we have encountered situations when patients drew dermatologist's attention on spontaneous dotted repigmentation when taking specific pharmaceuticals (for examples, hepatoprotectors). Undoubtedly, such facts should be retrieved, and patient might be recommended to visit a respective medical specialist, and inclusion of such drugs into individual vitiligo treatment scheme should be considered.

Finally, a patient should be warned that treatment course is lengthy, staged and begins with the less aggressive (i.e., safe) and less expensive options. "Treatment step" (which is defined as a time from starting a particular therapeutic scheme until first examination when it is reasonable to preliminary evaluate success of the treatment or lack of it) usually takes 3 months. Each step should continue for a substantial time span as repigmentation is usually a slow and lengthy process, and upon efficient therapeutic response of skin, current therapeutic scheme should be kept in force until maximal repigmentation of vitiligo lesions is achieved, which might take 1 to 2 years.

**The beginning.** When vitiligo treatment begins, all patients receive a course of immunocorrecting therapy with Neovir (Pharmsintez, Russia). Prescription of Neovir is especially feasible when dealing with progressing vitiligo. Neovir (sodium 10-methylene-carboxylate-9-acrydone) belongs to low molecular weight synthetic immunomodulators - interferon inducers. The drug is prescribed in a form of injection (2 ml of 12.5% solution intramuscularly every 48 hrs, 10 injections). In the future, upon stable vitiligo course, Neovir is administered as prophylactics annually as described above.

Along with Neovir, patients are prescribed: folic acid, 1 mg daily for 3 months; vitamin B6 (pyridoxine), 10 mg trice a day for 3 months; essential phospholipids, 2 caps twice daily with meal for 1 month. In spring and summer, when sun activity is high, all patients receive antioxidants: Dehydroquercitin, 1 pill a day for 3 to 5 months; or Cardiomagnyl (acetylsalicylic acid), 75 mg once daily, 3 to 5 months.

**First-line therapy.** As a first-line therapy, vitiligo patients are prescribed topical calcineurin inhibitors (Protopic 0.1% ointment, twice daily for 3 months). If pronounced clinical effect is seen, the treatment is continued until complete (or maximally achieved) repigmentation of vitiligo lesions.

Instead of calcineurin inhibitors, topical medium-potency corticosteroids can be used, such as betamethasone cream (Celestoderm, etc.), twice daily for 3 months. Upon pronounced effect, the treatment is continued until complete (or maximally achieved) repigmentation of vitiligo lesions. Also, topical preparations containing corticosteroids and vitamin D<sub>3</sub> analogues (such as Daivobet) can be used by the same scheme. Taking into account local side effects of corticosteroids, especially when applied on the face, we tend to recommend initial vitiligo treatment with topical calcineurin inhibitors.

**Second-line therapy.** The second-line therapy is applied when the first-line treatment fails to show clinical efficiency after 3 months of endorsement.

As the second-line therapy for vitiligo, we recommend phototherapy with narrow-band ultraviolet B (NB-UVB) with 311 nm wavelength. NB-UVB, especially when combined with first-line therapy drugs, allows for reaching maximal clinical effect. It should be kept in mind that for pronounced clinical effect, 100 to 200 phototherapy sessions might be required. Also, phototherapy has several contraindications such as oncological processes, cataract, etc., and requires regular (usually 3 times a week) visits to clinic which is inconvenient for many patients or even impossible owing to lack of dedicated equipment in regional clinics. In the case of localized vitiligo, NB-UVB can be administered at home settings using special hand-held NB-UVB lamps designed for home use which is convenient from the patient's side and does not require repetitive visits to a clinic.

**Third-line therapy.** If no effect is seen without 3 months since implication of the second-line therapy, it is feasible to switch to the third-line treatment.

As a third-line therapy, we recommend psoralen-ultraviolet A (PUVA) therapy. In some patients, PUVA shows better efficiency than NB-UVB, especially when combined with topical calcineurin inhibitors or corticosteroids (first-line treatments). This type of treatment, similar to NB-UVB, is lengthy (100-200 sessions) and has the same contraindications and inconvenience.

**Forth-line therapy.** To the forth-line therapy of vitiligo we ascribe excimer laser with 308 nm wavelength. This type of therapy also can be used as a third-line option when dealing with localized vitiligo. Excimer laser phototherapy can be endorsed as a monotherapy or in combination with topical pharmaceuticals used as a first-line treatment. At average, from 45 to 100 sessions (tree times a week) are required to restore pigmentation.

**Fifth-line therapy.** The fifth-line therapy is not universal and is applicable when depigmentation area is limited, and vitiligo is characterized by a stable course at least over a preceding year. In this case, intradermal administration of corticosteroids in lesions can be used, or injections of enriched by thrombocytes autoplasm can be applied in a form of intradermal injections every 2 weeks, at total for 12 procedures or until improvement.

Besides the described above therapeutic schemes, when necessary, vitiligo patients can receive pharmacological psycho-vegetative correction by neuroleptics, anti-depressants and tranquilizers (commercially available brands Sonapax, Neuleptil, Azafen, Relanium, Dopegit, Novo-Passit, glycine- containing preparations).

## CONCLUSIONS

The above described strategy of vitiligo management allows for efficient treatment of the disease in motivated patients, while avoiding frequent premature terminations of treatment due to lack of motivation or because of unjustified expectations of quick treatment results. The described algorithm allows for reaching pronounced repigmentation of vitiligo lesions in 80-90% of cases and assures long-term, often lifetime, remission of vitiligo.

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