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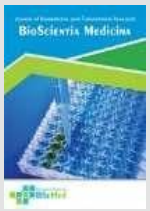

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Pulse Dose Corticosteroid Therapy in Vitiligo: A Narrative Literature Review

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A B S T R A C T

Vitiligo is an idiopathic skin depigmentation disorder with clinical symptoms of macules and depigmented patches on the skin. Vitiligo is a multifactorial disorder associated with genetic and non-genetic. There are two types of vitiligo: non-segmental and segmental vitiligo. The type of vitiligo can be determined based on physical examination and affects the disease course, prognosis, and therapy response. Vitiligo management is still a challenge on its own because the etiology is not clear, and many factors must be considered in the vitiligo treatment. Vitiligo management greatly varies depending on the activity and the disease expansion. The goals of vitiligo treatment include stopping disease progression, increasing repigmentation, and preventing recurrence. Vitiligo therapy options vary widely, but none have been effective in treating vitiligo with a high recurrence rate. One of the vitiligo treatment options is systemic corticosteroids given in pulse doses bringing the effect of decreasing the vitiligo progression and minimizing side effects. This literature review aims to determine the use of pulse dose corticosteroid therapy in vitiligo.

1. Introduction

Vitiligo is an acquired skin depigmentation disorder, idiopathic, and can affect all ages and sexes.[1] Research on the vitiligo causes is still ongoing. The most widely proposed theories of vitiligo etiology include autoimmune, oxidative stress, and viral infection existence.[2] Research by Diana et al. in 2018 stated that the prevalence of vitiligo in the Dermatology and Venereology polyclinic of Dr. Moewardi General Hospital Surakarta stated that 108 people or 0.46% experienced vitiligo with a male frequency of 52.78%.[3]

Vitiligo management aims to stabilize the disease and increase repigmentation. Vitiligo therapy options vary widely, but none have been effective in decreasing the recurrence of vitiligo. The use of systemic corticosteroids has been reported to be effective in vitiligo, especially unstable vitiligo. Systemic corticosteroid therapy aims to inhibit the progression of the depigmentation process, stabilize vitiligo lesions and reduce the recurrence rate.[4] This literature review aims to determine the use of pulse dose corticosteroid therapy in vitiligo.

Definition

Vitiligo is an autoimmune skin disease caused by melanocyte dysfunction causing skin depigmentation.[4] It is also defined as a disease characterized by ivory-white or chalky white macules on the surface of the skin.[5] Hair involvement in vitiligo causes the hair to turn white.[6] Vitiligo is stable, i.e.,

no new lesion is found, and no lesion spreads for 12 weeks, whereas vitiligo recurrence is characterized by the appearance of more than 3 new lesions for 3 months after the disease activity cessation.[7] Vitiligo stability is defined as the new lesion absence or old lesion expansion or the Koebner phenomenon absence in the first year, and the disease is regressive for two months until two years. The duration of stable vitiligo is debated, but the average ranges from 6 months to 2 years.[8]

Pathogenesis

Vitiligo is a multifactorial disorder associated with genetic and non-genetic. The absence of functional melanocytes due to melanocyte destruction is a widely accepted theory. The complex and different etiology of each vitiligo patient causes many theories to be combined so that they can explain the vitiligo occurrence, including genetic, autoimmune, and oxidative stress theory (Figure 1).[9]

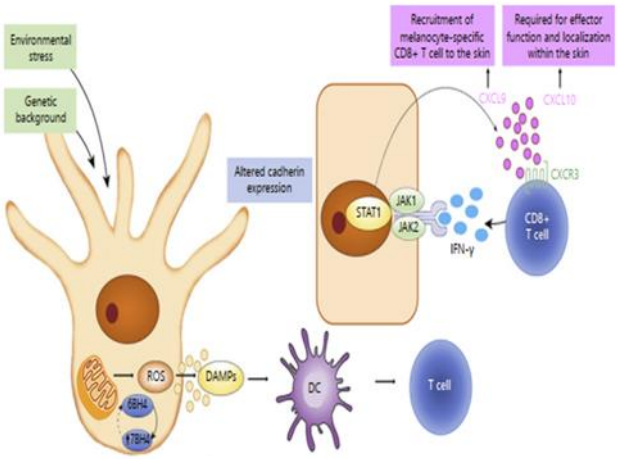

Figure 1. Patogenesis vitiligo. (CXCL: chemokine ligand; CXCR: chemokine receptor type; JAK: janus kinase; STAT: signal transducer and activator of transcription; DC: dendritic cell; ROS: reactive oxygen species; 6BH4: 6-tetrahydrobiopterin; 7BH4: 7-tet-rahydrobiopterin; DAMPs: damage-associated molecular pattern).[10]

Clinical manifestation

Vitiligo is characterized by macules and white patches without scales with clear boundaries and no symptoms such as itching and pain. Vitiligo lesions can affect the whole body with a symmetrical distribution. It can affect the body, face, acral and genital areas. The specific lesion in vitiligo is divided into acrofacial, mucosal, generalized, universal, and mixed lesions.[7] The skin and hair follicles depigmentations are vitiligo hallmarks. The Segmental type is vitiligo which has rapid progression and stabilization. Disease progression is characterized by the inflammatory phase existence, trichome lesion, and confetti-like lesion or Koebner phenomenon. The inflammatory phase is a brief phase causing rapid depigmentation with the characteristic of erythema existence, scaling, and itching in a hypopigmented or depigmented area with an erythematous margin. A trichome lesion is a lesion that has 3 colors, including depigmented lesion, normal skin, and hypopigmented zone.[11] Confetti-like depigmentation is a sign of vitiligo progression because it has a vitiligo disease activity score (VASI) and is associated with active, progressive, and aggressive vitiligo.[11] Vitiligo global issues consensus conference (VGICC) in 2011 in France issued a consensus on the vitiligo classification (Table 1).

Table 1. The vitiligo classification.[11]

Vitiligo type	Clinical manifestation
Vitiligo non segmental (VNS)	Depigmented lesion involves the face, body, and extremities in a symmetrical pattern
Generalized vitiligo	
Acrofacial vitiligo	Depigmented lesion confines to the face, head, hand, and distal feet
Mucosal vitiligo	Oral and/or genital mucosal involvement. Mucosal vitiligo is classified as VNS vitiligo if followed by skin involvement and as indeterminate vitiligo if there is no skin involvement.
Universalis vitiligo	Depigmented lesion covers 90% of the body surface area
Mixed vitiligo	Depigmented lesion with segmental vitiligo predilection followed by VNS
Punctate vitiligo	Depigmented lesion is with the confetti-like appearance
Vitiligo segmental (VS)	
Vitiligo interdeterminan	

Dermoscopy examination in vitiligo

A Dermoscopy examination of vitiligo is one of the ways that can be used to establish a vitiligo diagnosis. Dermoscopy functions to assess the disease stage in vitiligo, such as stability, progression, repigmentation, and therapy success. Dermoscopy findings were associated with vitiligo disease activity (Table 2). Dermoscopy features of pigmentary change include perifollicular pigmentation, reticular hyperpigmentation, marginal hyperpigmentation, and pigment network change. Specific dermoscopy examination shows disease activity, including leukotrichia, polka dots, starburst appearance, Koebner micro phenomenon, erythema, and telangiectasia (Figures 2 & 3).[12, 13]

A Dermoscopy examination is useful not only to establish a diagnosis of vitiligo but also to evaluate disease activity and assess the response of therapy. It is also useful in differentiating vitiligo from other hypopigmented and depigmented disorders. Morphological criteria assessed at dermoscopy include blood vessels, bleeding, ulceration or erosion, and follicular damage.[12]

Table 2. Dermoscopy finding dan vitiligo activity.[12]

No.	Dermoscopy finding	Relevance to disease activity
1.	Starburst appearance	Progressive disease
2.	Comet tail appearance	Progressive disease
3.	Micro-Koebner phenomena	Progressive disease
4.	Tapioca sago appearance	Progressive disease
5.	Perilesional/ marginal hiperpigmentasi	Stable vitiligo and repigmentation
6.	Eritema intra/ perilesional with telengiectasia	Stable vitiligo and repigmentation

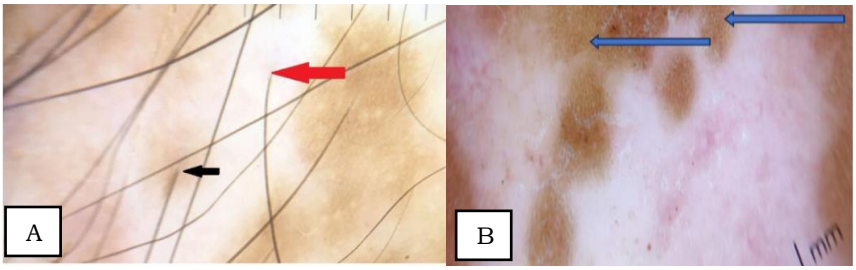

Figure 2. Dermoscopy description (10x magnification); (A) Pigmented perifollicular (black arrow) and depigmented perifollicular (red arrow)[12]; (B) Perilesional hyperpigmentation (blue arrow).[13]

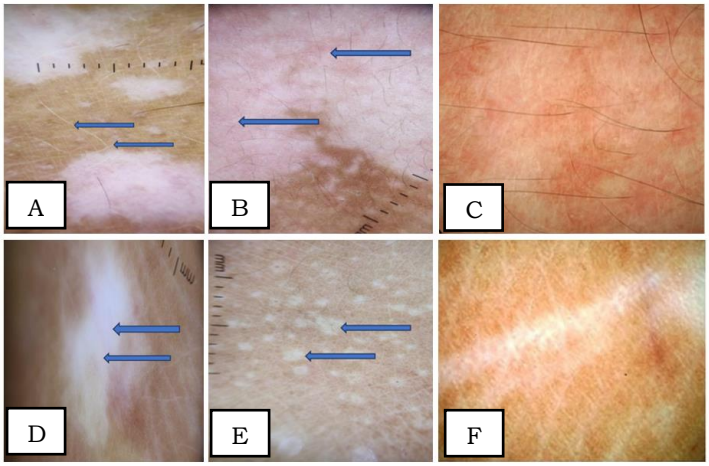

Figure 3. Dermoscopy description (10x magnification) A. Starburst pattern (blue arrow), B. Polka dots, C. Micro-Koebner phenomenon, D. Leukotrichia E. Erythema and telangiectasia, F. Altered pigment network.[12,13]

Pulse dose therapy in vitiligo

Vitiligo management is still a challenge on its own because the etiology is not clear, and many factors must be considered in the vitiligo treatment. Vitiligo management greatly varies depending on the activity and the disease expansion. The vitiligo treatment goals include stopping disease progression, increasing repigmentation, and preventing recurrence. Vitiligo with active progression requires a therapy combination including oral anti-inflammatory to prevent disease progression and phototherapy. Stable vitiligo requires single therapy such as topical corticosteroid or phototherapy because of slow disease progression.

Oral pulse dose corticosteroid therapy is defined as corticosteroid therapy given for 2 days a week to reduce the systemic corticosteroid side effects, whereas oral pulse dose therapy with a low dose is the smallest corticosteroid dose that can be given in pulse therapy.[14]

Oral corticosteroid is generally used as a short-term therapy in rapidly progressing vitiligo or unstable vitiligo. Rapid progression is defined as the appearance of more than 3 new lesions in 3 months. Oral corticosteroid is also second-line therapy in vitiligo patients that are not too responsive to topical and narrowband ultraviolet B (NBUVB) therapy.[7,15]

Indication and contraindication

Indication for systemic corticosteroid is the first line of therapy in unstable vitiligo. A corticosteroid helps suppress disease progression and induce repigmentation of peripheral lesions or perifollicular areas. The therapeutic assessment was carried out since the patient started therapy by taking photos as the baseline and evaluated every 4 weeks. Systemic corticosteroid therapy must be performed with gradual dose reduction if the vitiligo has been stable and added treatment modalities to increase repigmentation. Patients with slow vitiligo progression or body surface area >10% with persistent new lesions can also be given episodic systemic corticosteroid therapy for 8-12 weeks. Systemic corticosteroid is not recommended in stable vitiligo because corticosteroid is not a repigmenting agent. Systemic corticosteroid is also not recommended in vitiligo Universalis.[15] Absolute contraindications include systemic fungal infections and herpes simplex infections, while relative contraindications include heart failure, human immunodeficiency virus (HIV) infection, psychosis, peptic ulcer disease, active tuberculosis, and septicemia. A low dose of systemic corticosteroid can be given to patients with diabetes mellitus and controlled hypertension.[14]

Pulse dose corticosteroid administration

The purpose of this therapy is to provide a high dose of oral corticosteroid with minimal side effects. Systemic corticosteroids can induce immunosuppression. Corticosteroid agents used in vitiligo include prednisolone, methylprednisolone, and betamethasone or dexamethasone. The challenge of using oral corticosteroids is determining the dose and therapy duration so that it can increase repigmentation and minimize side effects. [5] The equivalent dose of systemic corticosteroid can be seen in Table 3.[15,16]

Table 3. Corticosteroid equivalent dose.[15]

Corticosteroid	Equivalent dose (mg)
Rapid action	
Cortisone	25
Hydrocortisone	20
Deflazacort	6
Intermediate action	
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Slow action	
Dexamethasone	0,75
Betamethasone	0,6-0,75

Pulse Therapy with a low dose

Pulse dose therapy with a low dose is the high dose corticosteroid therapy with intermittent administration and is a long-term maintenance therapy for 6 months by giving corticosteroid 2 consecutive days for a week followed by five days free of therapy. Long-acting corticosteroid is chosen as the pulse dose therapy regimen with low dose because it takes effect within 3 days. Cotyrotropin and cortisol levels will rapidly decrease after the second dose and return to the baseline before the next pulse dose. The option of giving 2 consecutive days for 1 week is chosen than giving once every 3 days because the hypothalamic-pituitary-adrenal axis (HPA) has a rest period to return to a normal level before the next dose.[15]

The standard regiment used is 5 mg oral betamethasone after breakfast on Saturdays and Sundays or other days of the week or dexamethasone at a 5 mg or 10 mg dose. The pulse dose therapy can be increased to 7.5 mg if there is no response to treatment in adults, and the dose is reduced to 2.5-4 mg in children. Dosage in children aged < 4 years is recommended to use modified pulse therapy with a low dose of 1 mg using dexamethasone or betamethasone was given every 10 kg of body weight. Corticosteroid in pregnancy has category C, i.e., experiment on animal causes side effects on the fetus, and there is no evidence of human studies.[15]

The administration of pulse dose therapy with a low dose in vitiligo was first done by Parischa et al. in 1989 was evaluating five different regimens for four months to increase repigmentation and stop disease activity. Clinical improvement can be seen after administration of 3 mg of betamethasone orally, alternately combined with levamisole and topical fluocinolone or 2 mg oral betamethasone or alternately with 20 mg of 8-methoxy psoralen and sun exposure and dose pulse therapy with low dose consisting of 5 mg oral betamethasone twice weekly combined with 50 mg oral cyclophosphamide per day showed 87.5% repigmentation and 53.8% reduction in disease activity. The administration of a single dose of 5 mg betamethasone after breakfast for 2 days a week for 1-3 months can reduce disease progression: by 89% and induce spontaneous repigmentation in patients with rapid and extensive disease progression.[15,17]

Searle et al. in 2020 in Denmark stated that betamethasone or dexamethasone at 5 mg dose given for two days a week for 2 months could reduce disease progression; by 89% and repigmentation; by 80%.[4] Manga et al. in 2016 in New York stated that the use of dexamethasone at a low dose and as pulse therapy at a low dose of 2.5 mg daily twice a week could reduce vitiligo activity; 91.8% for 13 weeks.[18] Oral steroid pulse therapy with a low dose produces good repigmentation if combined with NBUVB.[16,19]

The phototherapy combination with pulse dose therapy with a low dose at a dose of 0.1 mg/kg body weight of betamethasone given two consecutive days in a week proved to be effective in increasing repigmentation in 18% if compared to single phototherapy in 8%. Majid et al. in 2009 in Egypt conducted a study on 400 children with progressive vitiligo using oral methylprednisolone at a dose of 0.8 mg/kg body weight with 32 mg maximum dose, given two consecutive days per week for 6 months, showed a reduction in progression in 90% and repigmentation in 65.5%. Total repigmentation in a 5-year-old child using 2.5 mg betamethasone twice a week for three months, and no side effects were reported.[20]

The study by Radakovij-Fijan et al. in 2001 in Austria using pulse dose therapy with a low dose of 10 mg dexamethasone in two consecutive days per week followed by discontinuation of five-day therapy for 24 weeks showed a reduction in disease activity in 88% in 18 weeks after therapy. Radakovij-Fijan stated that pulse dose therapy with low doses was an effective therapy for stopping disease activity but had a weak potential to induce repigmentation. Pulse dose therapy with a small dose of corticosteroid should be used in combination therapy to increase the repigmentation effect.[17,21,22]

Recurrence of vitiligo lesions after discontinuation of pulse dose therapy with low doses is rare. The study by Passeron et al. in 2017 in France in 138 children treated with pulse dose therapy with a small dose of methylprednisolone for 6 months showed recurrence in 34.8% for one year, but recurrence in children aged < 10 years was 47.7%.[23]

Intravenous pulse dose therapy

Intravenous pulse dose therapy is generally given using methylprednisolone 8 mg/kg body weight intravenously for three consecutive days in one month. It can inhibit the spread of vitiligo and induce spontaneous repigmentation. The administration of pulsed intravenous therapy is safe for patients with hypertension.[15] Methylprednisolone is a moderately acting anti-inflammatory agent and has lower power of inducing sodium and water retention if compared to hydrocortisone. The methylprednisolone dose is 20-30 mg/kg or 500-1000 mg/m^2 per intravenous pulse dose with a maximum dose of 1 gram.[24,25]

Dexamethasone can also be used as an intravenous pulse dose therapy at a dose of 4-5 mg/kg body weight or 100-200 mg per beat. The method of administering intravenous pulse doses is by inserting an intravenous corticosteroid for 10-20 minutes, but this method increases the risk of hemodynamic abnormalities. Another way is by dissolving systemic corticosteroid in 150-200 ml of 5% dextrose and slowly infusing it intravenously for 2-3 hours.[24-26]

The study conducted by Seiter et al. in 2000 in Germany administered intravenous pulse therapy to 14 patients with generalized vitiligo using methylprednisolone 8 mg/kg body weight, three consecutive days for one month showed a reduction in disease progression in 85% of patients and 71% repigmentation.[27] The research by Nagata et al. in 2014 in Japan gave 500 mg of methylprednisolone intravenously, three consecutive days, three times per month showed disease cessation if examined by spectrophotometry.[28] Lee et al. 2007 in Korea conducted a study by providing combination therapy in 500 mg methylprednisolone intravenously for three consecutive days, then continued twice a week with PUVA showed 50% repigmentation.[29]

Side effect

Systemic corticosteroid has a variety of side effects. The side effects of systemic corticosteroids depend on the dose, therapy duration, and individual susceptibility. Evaluation of clinical symptoms and

side effects can minimize more serious side effects and can be a consideration for therapy continuation. The side effects of systemic corticosteroids based on dose include hyperglycemia, hyperlipidemia, peptic ulcer disease, and psychosis. The side effects based on duration consist of hypertension, striae, tachyphylaxis, Cushing syndrome, telangiectasia, failure to thrive, osteoporosis, ochronosis, and opportunistic infection. Steroid withdrawal symptoms are the symptoms appearing as the result of spontaneous discontinuation of high-dose systemic corticosteroid. These symptoms include weakness and myalgia and generally with corticosteroid doses of more than 20-30 mg of prednisolone. High doses of corticosteroids can also cause adrenal crisis due to extreme suppression of the adrenal glands. Cushingoid change includes facial swelling, moon face, buffalo hump, striae, hair growth, and skin atrophy increase (Table 4).[15]

Table 4. Systemic corticosteroid side effects.[15]

Influenced system	Side effect
HPA Axis	Steroid withdrawal syndrome, additional crisis
Metabolic	Hyperglycemia, appetite and weight increase, hypertension, congestive heart failure, hypokalemia, hypertriglyceridemia, Cushingoid changes,
Bone	Osteoporosis, osteochronosis, hypokalemia
Gastrointestinal	Peptic ulcer disease, intestinal perforation, fatty liver degeneration, esophageal reflux, nausea, and vomiting
Psychiatry	Psychosis, agitation, depression, agitation
Eye	Cataract, glaucoma, infection
Nerve	Pseudomotor cerebral, peripheral neuropathy
Muscle	Myopathy
Skin	Inhibited wound healing, acneiform eruptions, purpura, skin infections, telogen effluvium, hirsutism, acanthosis nigrican

2. Conclusion

The management is still a challenge because the etiology is not clear, and therapy depends on the activity and the disease expansion. The goals of vitiligo treatment include stopping disease progression, increasing repigmentation, and preventing recurrence. Systemic corticosteroid is an option for vitiligo treatment but is not recommended as the first-line therapy for vitiligo. Risk and side effect assessment of systemic corticosteroid use should be assessed, and the use of low-dose corticosteroid pulse therapy should be combined with combination therapy to increase the repigmentation effect.

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