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Systemic Corticosteroids in Vitiligo

Binod K. Khaitan and Sushruta Kathuria
Department of Dermatology and Venereology
All India Institute of Medical Sciences, New Delhi
India

1. Introduction
Vitiligo is an acquired disorder characterized by depigmented macules on skin, hair, and mucosa. Its prevalence worldwide is 0.1-2% and varies from country to country.1 It is associated with high psychiatric morbidity and dysfunction, particularly in darker skin types where the contrast between normal and depigmented skin is highly pronounced.2,3 The usual approach to the treatment of vitiligo has been to regain pigment in vitiliginous areas rather than controlling the disease process. This is akin to treating the effects of the disease rather than treating the disease itself. Such an approach frequently results in frustration because patients can continue to develop new lesions at other sites even while existing lesions are repigmenting, or the disease may be reactivated at a later stage even after achieving a fair degree of therapeutic success.4 Therefore, the important priority for the treatment of vitiligo should be first to control the disease process, and then taking measures to repigment existing lesions.

Systemic corticosteroids are a broad group of drugs that are widely used in various dermatological and non-dermatological conditions. Corticosteroids, both topical and systemic, have been used in vitiligo for over four decades with some concern about its efficacy as well as its known or expected adverse effects. Further research may provide evidence that systemic corticosteroids may be an important modality for the treatment of progressive vitiligo.

2. History
In 1967, oral corticosteroids were used for the first time in vitiligo. Triamcinolone orally was found to have a synergistic effect with methoxypsoralen as compared to methoxypsoralen alone.5 In 1976, adrenocorticotropic hormone (ACTH) was found to be effective in inducing repigmentation in patients who had previously failed phototherapy with psoralen followed by UVA exposure (PUVA).6 In the same year, a mixture of prednisolone, betamethasone, paramethasone acetate and methylprednisolone given orally was effective in producing satisfactory repigmentation in one-third of patients studied, thus confirming the efficacy of corticosteroids in vitiligo.7 Treatment of vitiligo is known to be long-term, hence the question of long-term safety of systemic corticosteroids is an important consideration. To reduce long-term complications of corticosteroids, oral mini-pulse therapy was introduced in 1989 and was established in 1993, where instead of daily oral corticosteroids, a long-acting
corticosteroid was given on two consecutive days of the week.\textsuperscript{5,9} Since then, systemic corticosteroids are used in day-to-day practice in extensive and progressive vitiligo.

3. Structure and classification

The structure of corticosteroids consists of three hexane rings and one pentane ring known as the cyclopentanoperhydrophenanthrene nucleus. The different systemic corticosteroids are variations of this basic structure. Systemic corticosteroids are classified according to their half-lives. (Table 1)

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Equivalent dose (mg)</th>
<th>Glucocorticoid potency</th>
<th>Mineralocorticoid potency</th>
<th>Plasma half-life (minutes)</th>
<th>Biological half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>2+</td>
<td>30-90</td>
<td>8-12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>2+</td>
<td>60-120</td>
<td>8-12</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>6</td>
<td></td>
<td></td>
<td>90-120</td>
<td>&lt;12</td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>1+</td>
<td>60</td>
<td>24-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>1+</td>
<td>115-212</td>
<td>24-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>180</td>
<td>24-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>78-188</td>
<td>24-36</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>20-30</td>
<td>0</td>
<td>100-300</td>
<td>36-54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6-0.75</td>
<td>20-30</td>
<td>0</td>
<td>100-300</td>
<td>36-54</td>
</tr>
</tbody>
</table>

Table 1. Classification of Corticosteroids\textsuperscript{10,11}

The structure, mechanism of action, and pharmacokinetic profile of various systemic corticosteroids are similar. The main difference is in their glucocorticoid and mineralocorticoid effects and biological half-life. Hence, the choice of corticosteroid is decided by the duration of action needed, the dosing schedule to be used (daily versus weekly) and the clinical profile of the patient. Having a working knowledge of equivalent dosing helps in dose conversion when one corticosteroid is switched to another.

4. Mechanism of action of corticosteroids in vitiligo

Vitiligo is considered to be primarily an autoimmune condition that results in the loss of melanocytes. Melanocytes are lost in vitiligo due to the destruction of melanocytes by humoral or intrinsic cellular mechanisms.\textsuperscript{12} Humoral mechanisms involve destruction of melanocytes by pathogenic autoantibodies directed against melanocytes and the tyrosinase enzyme. Cellular mechanisms are as important as humoral in destroying melanocytes. Biopsies from vitiligo lesions show mild mononuclear infiltrate in the margins of lesional skin in active vitiligo with or without basal vacuolization. Active lesions show increased numbers of CD4\textsuperscript{+} T cells and increased epidermal expression of ICAM-1.\textsuperscript{13} Peripheral T-cell activation is also seen in nonsegmental vitiligo and T-cell dysregulation is not only limited to the lesions.\textsuperscript{14} The peripheral blood of vitiligo patients express more of the cutaneous
lymphocyte-associated antigen positive melanocyte-specific cytotoxic T lymphocytes indicating that there is recruitment of T cells in the circulation to the skin.\textsuperscript{15} Both the CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells from perilesional and non-lesional skin in vitiligo show polarization towards the Type 1 cytokine profile which parallels depigmentation.\textsuperscript{16} The melanocyte-specific cytotoxic T cells found in perilesional biopsies have the ability to infiltrate normal skin and destroy the melanocytes.\textsuperscript{17} Besides cytotoxic T cells, regulatory T cells (T regs) also have a role in vitiligo. The T reg population is not decreased in the peripheral circulation, however, these T regs are not able to settle in the skin and this defect seems to be crucial in the observed perpetual anti-melanocyte reactivity in progressive disease.\textsuperscript{18} Corticosteroids suppress autoantibody formation and likely induce apoptosis of cytotoxic T cells. The autoimmune hypothesis still prevails in the pathogenesis of non-segmental vitiligo, and the autoimmune process is not limited to the skin. In progressive disease, there is continuous assault on melanocytes. Topical corticosteroids, tacrolimus or any other topical agent may suppress autoimmune dysfunction at the site of a vitiligo lesion, but these do not have any effect on the disease process per se. Phototherapy and phototherapy stimulate melanocytes to cause repigmentation and have minimal immunomodulatory action on T-lymphocytes, but may not halt the rapid destruction of melanocytes. Systemic corticosteroids act not only on lesional immune activity, but also on the T cells in peripheral circulation. Besides modulating cell-mediated immunity, corticosteroids also suppress autoantibody formation. The serum of actively spreading vitiligo patients who received oral corticosteroids and showed improvement had a decrease in complement-mediated cytotoxicity by melanocyte autoantibodies and a reduced antibody titer to the melanocyte surface antigen.\textsuperscript{19}

5. Indications

Systemic corticosteroids are the first-line treatment when a patient presents with rapidly progressive vitiligo. It helps not only in halting progression of the disease, but also induces repigmentation as normal melanocytes from the periphery of the lesions or perifollicular area take over, once the process of melanocyte destruction is arrested. Assessment of treatment response is important and since the patient is not always sure whether new lesions have appeared or not since corticosteroid initiation, a baseline photographic record must be taken before starting treatment and periodically throughout treatment, preferably at 4-week intervals. The time taken for disease activity to stop is variable and may range from a few weeks to months. Once stability is achieved (defined as no new lesion formation and no extension of existing lesions), one must taper the corticosteroids slowly and add other modalities for augmentation of repigmentation.

Patients with extensive slowly progressive vitiligo (body surface area more than 10\% with the continuous appearance of new lesions or slow extension of existing lesions) may also benefit from systemic corticosteroids as this suggests “simmering” autoimmune activity that may be long-term. Besides maintenance therapy, episodic treatment for 8-12 weeks at a time can also be added whenever there is relapse.

For example, systemic corticosteroids can also be added to photochemotherapy or phototherapy when there is transient fluctuation or worsening of disease activity. It can also be an adjuvant to surgery in both segmental and nonsegmental vitiligo.\textsuperscript{20,21} It is not advisable to use corticosteroid monotherapy in segmental vitiligo because segmental vitiligo is known to stabilize after some time. The initial period of progression
may be rapid in segmental vitiligo, but nearly all lesions stabilize and remain confined to one part of the body. Hence use of corticosteroids may not be advisable. Patients with stable vitiligo will also not benefit from corticosteroids because they are not simply repigmentation agents; rather their efficacy comes from their effects on active disease. Universal or near-universal vitiligo is also not an indication for the use of corticosteroids since treatment is usually depigmentation of residual pigmented areas.

6. Modes of administration

Systemic corticosteroids given orally are effective in halting progression of vitiligo and producing repigmentation. However, the long treatment duration required in vitiligo raises concern about the long-term cumulative side effects of corticosteroids. Daily doses or alternate day dosing is thereby avoided in vitiligo. Therefore, oral mini pulse therapy (OMP) is preferred for the planned long-term maintenance therapy for 6 months or beyond.9 OMP refers to giving a higher than the usual daily dose of corticosteroid on two consecutive days a week and leaving the remaining five days treatment-free. A long-acting corticosteroid is preferred so that the effect lasts for about 3 days at a time. Corticotropin and cortisol levels fall rapidly after the second dose of drug, but returns to baseline before the next dexamethasone pulse.22 Hence, it is preferred to give a long-acting corticosteroid on two consecutive days in a week rather than once in three days to give the hypothalamic-pituitary-adrenal axis (HPA) axis time to revert back to normal before the next dose. The standard regimen is to give oral betamethasone 5 mg (5 of the 1 mg betamethasone tablets) after breakfast on Saturday and Sunday (or any other two consecutive days) every week.9 Dexamethasone pulse has been used in doses of 5 mg or 10 mg in this manner.22,23 Betamethasone pulse has been given as an adjunct with surgery.24 Besides this standard regimen, there can be variations in OMP. If no response is seen, the dose can be increased from 5 mg upto 7.5 mg. In children, dose is reduced from 5 mg to 2.5-4 mg. Additional immunosuppressants, for example, cyclophosphamide and azathioprine, may also be added to the therapeutic regimen. Methylprednisolone25 has been used intravenously as high dose pulse therapy given on 3 consecutive days in a month but should not be considered as first-line treatment. Daily low dose prednisolone has also been used in tapering doses to discontinuation.26,27 The intramuscular route is not preferred as it is painful, and the level of drug in the circulation is unpredictable and good results are achieved by oral administration.

Monitoring of weight, fasting blood sugar, and blood pressure every month is necessary for any patient on systemic corticosteroids. Baseline and periodic photographs should also be done to monitor treatment response and repigmentation.

7. Side effects and contraindications

Systemic corticosteroids are known to have a variety of adverse effects. The predominant side effects are described in Table 2. However, these adverse effects do depend on dose, duration of treatment, and individual susceptibility. All patients do not develop the same adverse effects. Therefore, clinical evaluation and monitoring is the best way to ascertain whether adverse effects are minimal or serious, and reversible or irreversible. Minimal and reversible side effects are acceptable for continuing treatment.
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System Affected | Side Effects
--- | ---
HPA Axis | Steroid withdrawal syndrome, Addisonian crisis
Metabolic | Hyperglycemia, increased appetite and weight gain, hypertension, congestive heart failure, hypokalemia, hypertriglyceridemia, cushingoid changes, menstrual irregularities
Bone | Osteoporosis, osteonecrosis, hypocalcemia
Gastrointestinal | Peptic ulcer disease, bowel perforation, fatty liver changes, esophageal reflux, nausea, vomiting
Ocular | Cataracts, glaucoma, infections
Psychiatric | Psychosis, agitation, depression
Neurological | Pseudotumor cerebri, peripheral neuropathy
Muscular | Myopathy
Cutaneous | Delayed wound healing, acneiform eruption, purpura, cutaneous infections, telogen effluvium, hirsutism, acanthosis nigricans

Table 2. Side Effects of corticosteroids

The primary consideration in treating vitiligo is careful patient selection in order to maximize response to vitiligo while minimizing adverse effects. The other concern is determination of proper dose and dosing schedule. Side effects can be dose- or duration-dependent. Dose-dependent side effects of corticosteroids are hyperglycemia, hyperlipidemia, peptic ulcer disease, and psychosis. Duration-dependent changes are hypertension, cushingoid changes, growth impairment, osteoporosis, osteonecrosis and opportunistic infections. Steroid withdrawal syndrome is observed when systemic corticosteroids given at high doses are abruptly stopped and it presents as vague symptoms of lethargy, generalized weakness and myalgia. Abrupt withdrawal of the corticosteroid does not give enough time for the suppressed HPA axis to recover. It is observed with doses higher than 20-30 mg of prednisolone. Duration of treatment is not a predictable causative factor. High dose of corticosteroid can also lead to extreme suppression of adrenals (Addisonian crisis) manifesting as hypotension and extreme weakness. Cushingoid changes occur with long term treatment and present as puffiness of face, moon facies, buffalo hump, striae, increased hair growth on face, skin atrophy, increased abdominal girth with thin extremities and others. Growth impairment and opportunistic infections can be decreased by avoiding daily administration either by using alternate day dosing or OMP. Oral mini pulse therapy has fewer side effects (e.g., moon facies, weight gain, acne) compared to daily dosing as reviewed in a meta-analysis. Betamethasone and dexamethasone can be used interchangeably as the potency and half-life are almost same. When compared to other corticosteroids, deflazacort is considered to have relatively fewer cases of growth retardation in children, osteoporosis, weight gain and HPA axis suppression.

Absolute contraindications to use of systemic corticosteroids are very few, and include such conditions as systemic fungal infections and herpes simplex keratitis. Relative contraindications are congestive heart failure, human immunodeficiency virus (HIV), psychosis, active peptic ulcer disease, active tuberculosis, and septicemia. Well-controlled diabetes and hypertension are not contraindications, but lower doses should be used, the
concomitant disease must be adequately treated, and the patient should be monitored frequently.

There are various approaches to minimize the side effects of corticosteroids. First is to give corticosteroids only as long as disease activity is present and taper it slowly (over a period of 3-6 months) when no indication of new lesions are present. The oral mini pulse therapy regimen has significantly less side effects compared to typical daily dosing of corticosteroids. An important finding is the lack of prolonged HPA axis suppression with OMP therapy. Furthermore, higher doses of dexamethasone (10 mg) do not seem to provide any additional benefit to 5 mg betamethasone. Choosing corticosteroids with less risk of mineralocorticoid-type effects (i.e., dexamethasone, betamethasone) or one with supposedly fewer side effects (i.e., deflazacort) can be beneficial for all patients. Calcium supplementation, salt restriction, proper diet, daily exercise and use of antacids can minimize risk of side effects. Regular monitoring of weight, fasting blood sugar, and blood pressure will help in early detection of side effects if they occur.

8. Safety in children and pregnancy

The decision to treat progressive vitiligo in children below 4 years of age can be rather difficult as limited data is available for this population. It is suggested that oral mini pulse therapy be modified (i.e., 1 mg of dexamethasone or betamethasone given for every 10 kg) and used.

Corticosteroids have been safely used in pregnancy and are classified as category C drugs (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). However, it is best to reserve its use in pregnancy when the benefits of treatment outweigh the risk of side effects. Pregnancy is known to precipitate and aggravate vitiligo. However, vitiligo being a non-life threatening condition, a patient may defer any type of treatment, including corticosteroids.

9. Efficacy of corticosteroids in vitiligo

Worldwide, there are few studies published documenting the efficacy and safety of corticosteroids in vitiligo. The available reports are primarily case series and there is a lack of well validated randomized controlled trials.

9.1 Oral mini pulse therapy

Pasricha et al evaluated the effect of five different regimens in causing repigmentation and stopping disease activity for four months and noted that regimens using corticosteroids were superior to those excluding corticosteroids. Improvement with 3 mg betamethasone orally on alternate days combined with levamisole and topical fluocinolone, 2 mg betamethasone orally alternating with 20 mg 8-methoxypsoralen and sun exposure, and oral mini pulse consisting of 5 mg betamethasone orally twice a week combined with 50 mg cyclophosphamide daily orally was 87.5%, 85% and 90.9% respectively, while levamisole 150 mg two days a week showed improvement in 53.8%. Addition of topical fluocinolone acetonide to levamisole showed better response in 81.8%.

In a study on forty patients by Pasricha and Khaitan, 5 mg betamethasone as a single oral dose after breakfast on 2 consecutive days per week was found effective in halting disease
progression in 89% patients within 1-3 months and inducing variable spontaneous repigmentation in patients with extensive and rapidly progressive disease. Only 2 patients did not show response initially, but once the dose was increased from 5 mg to 7.5 mg, there was notable improvement. Side effects were seen in 23% (17) patients, such as weight gain (5), mild headache (2), transient general weakness (2), bad taste in mouth (3), acne (2) and mild puffiness, perioral dermatitis, as well as herpes zoster, glaucoma and amenorrhea, of which were reported in one patient each. Kanwar et al. and Radakovic-Fijan et al. also reported efficacy of dexamethasone oral mini pulse therapy in arresting progression of rapidly spreading vitiligo in 43.8% and 88%, respectively. The difference in response in this study by Kanwar et al and the one conducted by Pasricha and Khaitan could be because of the higher proportion of patients with segmental vitiligo and shorter duration of treatment in the Kanwar et al study.

OMP has been found to be effective in patients with unstable generalized and acrofacial vitiligo in a randomized double-blind placebo-controlled randomized prospective study. Prednisolone has been used as once a week oral dose of 2 mg/kg in 50 patients with extensive and rapidly spreading vitiligo. The disease progression was arrested in 93% and repigmentation observed in 88% with only 3 patients developing side effects. Methylprednisolone 0.8mg/kg given as OMP along with topical fluticasone in children for 6 months was safe and effective in arresting disease in 90% and producing variable repigmentation in 65%.

OMP in combination with other standard vitiligo treatments has also been studied. Betamethasone has been used as an adjunct to surgery for treatment of stable vitiligo patches in patients who did not respond to their first surgical. It has also been combined with phototherapy and photochemotherapy. Dexamethasone OMP has been found effective and safe with psoralen with solar ultraviolet light (PUVAsol) in fast spreading vitiligo. OMP has been safely used in children and was more effective than 8-methoxypsoralen alone. Combination of narrowband UVB (NB-UVB) with OMP has been compared with psoralen and ultraviolet A (PUVA) photochemotherapy with OMP. Disease progression is arrested in both, but repigmentation was better and earlier with NB-UVB.

Immunosuppressants can also be added to OMP. A comparison study of three regimens: (a) OMP with daily cyclophosphamide, (b) a 3-day dexamethasone-cyclophosphamide pulse given monthly, and (c) daily cyclophosphamide and dexamethasone-cyclophosphamide pulse given only on one day in a month showed that disease activity was arrested by all three modalities but repigmentation up to 75% was seen in 71%, 62%, and 53%, respectively. The higher response with OMP may be because weekly dosing may provide better immunosuppression in the context of vitiligo as compared to monthly dosing in pulse therapy. Weight gain was more frequent with OMP, but otherwise all three regimens had a similar frequency of side effects.

9.2 Daily corticosteroids

In everyday practice, corticosteroids are primarily administered daily at doses individualized for each specific patient. Published studies are based on prednisolone given at 0.3mg/kg as a single oral dose after breakfast initially for the first 2 months. The dosage is then reduced to half the initial dose during at the third month and halved again in at the fourth month of treatment. With this regimen, Kim et al noted that disease progression was halted in 87.7% of patients and in 70.4%, repigmentation was also seen. In a study by Banerjee et al, disease
progression was arrested in 90% and repigmentation was seen in 76%. The side effects observed in both studies were not serious, and did not warrant a change in dose or dosing schedule. Disease was also reported to completely subside after discontinuing treatment in addition to other positive observations; this suggests that low dose corticosteroids given for 4 months may be reasonably safe and effective treatment option.

9.3 Intravenous pulse therapy
Methylprednisolone (8 mg/kg) given intravenously on three consecutive days a month was used in a study as pulse therapy in 14 patients with generalized vitiligo. Eighty-five percent of the patients who presented with progressive disease showed cessation of disease progression and 71% of these patients had repigmentation. None of the six patients presenting with static disease showed any repigmentation. The therapy was well tolerated in all but one patient who developed intermittent arterial hypertension during therapy. Most studies indicate that systemic corticosteroids are helpful in halting disease progression in rapidly spreading vitiligo and inducing spontaneous repigmentation. However their role in static vitiligo is not well documented. As of now, corticosteroids can be recommended for rapidly spreading vitiligo for a short duration to halt disease activity, but it should not be used for repigmentation in static vitiligo, even if disease is extensive. Areas that require further research is the risk of osteoporosis with corticosteroids and the efficacy of calcium supplementation. Studies with longer follow-up periods are required to evaluate the potential for relapse. Deflazacort needs to be evaluated as a relatively safer corticosteroid option for vitiligo since its use in vitiligo is very limited. Head-to-head comparative studies between betamethasone, prednisolone, and deflazacort may be useful for determining the optimal agent for treatment.

10. Conclusion
There seems to be a definite role for systemic corticosteroids in the treatment of vitiligo. The types of vitiligo in which benefits have been observed are: (a) rapidly progressing vitiligo, (b) slowly progressing vitiligo with extensive involvement and frequent exacerbation, (c) frank inflammatory vitiligo, (d) patients with direct or indirect evidence of autoimmune disease (e.g., high titers of thyroid autoantibodies), (d) recalcitrant static vitiligo with exacerbation, and (e) rescue therapy. Corticosteroids should not usually be considered for universal vitiligo, segmental vitiligo or focal limited vitiligo.

Although daily or alternate day oral corticosteroids may be treatment options, OMP therapy seems to be the best regimen for long-term use with minimal side effects. The duration of OMP should be at least 6 months or longer and tapering to discontinuation should be slow and step-wise. When a patient is on any regimen that includes systemic corticosteroids, regular and periodic monitoring must be done to assess the risk-to-benefit ratio of treatment and to evaluate efficacy. Further study is needed to provide more definitive evidence for systemic corticosteroid use in vitiligo as well as the long-term implications of treatment.

11. References


Vitiligo: Management and Therapy is a practical guide to vitiligo that reflects current research related to the fundamentals of vitiligo and its management. Vitiligo experts and researchers from all over the world have contributed to this text, accounting for its comprehensive nature and diverse array of topics. The recent advances in medicine and technology have led to a better understanding of the disease and have broadened available treatment options. The essentials are captured in this book and are complemented by useful clinical photographs and reference tables. This concise tool will serve as an invaluable resource for clinicians in daily practice.

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