

Association of Drugs with Psoriasis: A Review of Literature

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Summary:

Psoriasis is a common disorder in dermatologic practice. Though its exact etiology is still unknown but there are many internal and external factors contributing to the clinical course of the disease. There are several drugs described in the literature that have been associated with the initiation, exacerbation and aggravation of psoriasis. Depending on the relation to induction or exacerbation of psoriasis the drugs may be classified as drugs with strong casual relation with psoriasis, drugs with considerable but insufficient

evidence of association and drugs with occasional association with aggravation or induction of the disease. Understanding of underlying pathogenesis is very important in the management of drug related psoriasis. This review included the most common causative agents in relation to psoriasis, their underlying pathogenesis, clinical manifestations and management of such cases.

Key words: psoriasis, etiologic agents of psoriasis, drugs related to psoriasis.

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Introduction:

Psoriasis is a chronic, noncontagious, multisystem, inflammatory disorder with a reported prevalence of 0.1 percent to 11.8 percent in different population.^{1,2} Psoriasis involves hyperproliferation of the keratinocytes in the epidermis, with an increase in the epidermal cell turnover rate. The cause of the loss of control of keratinocyte turnover is unknown. However, environmental, genetic, and immunologic factors appear

to play a role.¹ Some factors known to trigger psoriasis include smoking, alcohol consumption, body mass index (BMI), trauma, infection, endocrine disorders, drugs, and acute withdrawal of systemic or potent topical corticosteroids.³ Drug intake is a major concern in this respect, as new drugs are constantly being added to the list of factors that may influence the course of the disease.⁴ Analysis of comedication in a study of 1,203 psoriasis patients revealed 23.2 percent of patients were taking more than three systemic medications, and of these patients, 11.1 percent were taking more than 10 medications. Further analysis demonstrated that comorbid cardiac and metabolic disorders are common in these individuals with a high prevalence of hypertension (28.2%), diabetes (10.5%), and dyslipidemia (12.5%).³ With this in mind, many psoriasis patients can be on multi-drug regimens; therefore, careful analysis of medications that can exacerbate the disease is prudent.

Effect of drug on clinical course of psoriasis

Drug intake may affect the clinical course of psoriasis in the following ways

- Precipitation of de novo psoriasis in persons with or without a family history or predisposition of the condition.
- Exacerbation of pre-existing psoriasis
- Induction of psoriatic lesions on clinically normal skin in patients with psoriasis.⁴

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Types of cutaneous eruptions in relation to drugs

Psoriasiform drug eruption and Drug-provoked psoriasis are the two forms of cutaneous eruption that related to ingestion of several drugs. Psoriasiform drug eruption is a heterogeneous group of disorders that clinically and/or histologically simulate psoriasis at some point during the course of the disease. It may be a reaction to either the internal or the external

environmental, allergic, infective, parasitic, bacterial, fungal, viral and/or malignant stimuli. These psoriasiform reactions are elicited by inflammatory events that cause dysregulation of cytokines, growth factors, and abnormal keratinocyte proliferation.^{3,5} Drug-provoked psoriasis can be divided into two categories, drug-induced psoriasis and drug-triggered or aggravated psoriasis (Table-1).³

Table-I*Characteristics of drug induced and drug aggravated psoriasis. 3, 4, 6*

Drug induced psoriasis	Drug-triggered or aggravated psoriasis
Discontinuation of the drug will stop further progression of the disease.	The disease progresses even after discontinuation of the drug.
Tends to occur in a de-novo fashion in patients with no family or previous history of psoriasis.	Exhibits a propensity to occur in patients with a history of psoriasis or with a genetic predisposition for the disease.
The clinical presentation often mimic the pustular variant of psoriasis, often with no nail involvement or associated arthritis.	Patients can have exacerbation of pre-existing psoriatic lesions or develop new lesions in previously uninvolved skin.
There is an absence of Munro microabscesses, few macrophages, and sparse vascular changes on histology.	Histology reveals typical characteristic of psoriasis vulgaris.

Classification of Drugs in the development of psoriasis

Drugs can be divided into 3 categories in view of their relationship to drug-provoked psoriasis (Table II).⁴

Table-II*Drugs and their relationship in the development of psoriasis*

Category	Drugs/drug classes
Drugs with undoubted causal relationship to psoriasis	β -Blockers, lithium, syntheticantimalarials, nonsteroidal anti-inflammatory drugs, tetracyclines
Drugs about which there are considerable but insufficient data supporting induction or aggravation of psoriasis	ACE inhibitors, interferons, terbinafine
Drugs occasionally reportedto be associated with induction or aggravation of psoriasis	Clonidine, digoxin, amiodarone, quinidine, dihydropyridine calcium antagonists, carbamazepine, valproic acid (sodium valproate), fluoxetine, acetazolamide, sulfonamides, penicillin, amoxicillin, ampicillin, morphine, procaine, cimetidine, ranitidine, gold, mercury, oxandrolone, progesterone, gemfibrozil, potassium iodide, granulocyte-macrophage colony-stimulating factors

Beta-blocker

β -blockers are the most common drugs encountered in the exacerbation of psoriasis. β -blockers are classified as noncardioselective and cardioselective, according to interact selectively with β 1 and β 2 adrenergic receptors⁷.

- Cardioselective β -blocker- Practolol is the earliest in this group and has been most commonly cited in association with psoriasis. This drug was withdrawn because of many side effects including dermatological ones⁸⁻¹². Metoprolol¹³, Atenolol¹⁴ also reported to induce similar eruption.
- Noncardioselective β -blocker- Propranolol was reported to cause histologic changes in guinea pigs similar to those in psoriatic human skin. The eruptions described with propranolol use include psoriasis, psoriasiform dermatitis, eczematous and lichenoid rashes.^{15,16} Cetamolol¹⁷, nadolol¹⁸ also reported to cause similar eruption. Topical application of timolol, in the treatment of chronic open angle glaucoma was reported to induce psoriasis and to transform psoriasis vulgaris into psoriatic erythroderma.^{19,20,21}
- There is cross reactivity between b-blockers and probably every β -blocker is able to provoke psoriasiform eruptions, aggravation or induction of the condition.

Clinical findings

1. Latency period- Latency periods vary from several days to 12 months. Latency period is shorter in case of de novo pustular psoriasis and exacerbation of pre-existing psoriasis⁷.
2. β -blockers are responsible for the provocation of various clinical types of psoriasis. Psoriasiform eruptions are the most common consequences.^{4,21} Aggravation of classical psoriasis vulgaris and guttate psoriasis, transformation of plaque-type psoriasis into localized and generalized pustular psoriasis and rarely induction of classical plaque psoriasis.^{19, 22-24}

Pathogenesis

The precise pathogenic mechanism of the influence of β -blockers on the course of psoriasis is unknown. Several hypotheses have been proposed and investigated. These include decrease in intra-epidermal cyclic adenosine

monophosphate (cAMP) (it is the most reliable hypothesis so far), delayed type hypersensitivity, immunologic mechanism, impaired lymphocyte transformation.^{25, 26, 27}

β -adrenergic receptors are present in the skin and these receptors are blocked by β -blockers. Normal beta agonists' attachment to beta receptors resulting in increased cAMP levels is blocked by the beta antagonists. Cyclic AMP (cAMP), an intracellular messenger, stimulates proteins responsible for differentiation and inhibition of proliferation. A decrease in cAMP levels leads to a decrease in calcium and an up-regulation of keratinocyte proliferation, lack of differentiation, as well as an increase in lymphocyte motility seen in psoriasis.^{3, 4, 11, 28, 29} There is increased proteolytic enzymes released by macrophages, neutrophils, and lymphocytes. Proteolytic enzymes have been associated with keratinocyte hyperproliferation and psoriasiform eruptions.³⁰

Lithium

Lithium is a metal ion that has been used extensively in the treatment of manic-depressive disorder and in urology practice. The first association of lithium with psoriasis was suspected in 1972, and since then there have been several reports of lithium-induced psoriasis described in individuals with no personal or family history. Lithium-provoked psoriasis was first reported in 1976.^{31,32, 33} Psoriasiform eruptions are the most frequently reported cutaneous adverse effects of lithium treatment and reported to occur in 3.4 to 45 percent of patients treated with lithium.³¹

Clinical features

1. Latency period- Development of psoriatic lesions after the initiation of lithium treatment is variable and ranges from a few weeks to several months. The latency period is few weeks to months (average 20 weeks).^{7, 34}
2. Clinical manifestations of psoriasis aggravated or induced by lithium carbonate- Most common presentation is classic plaque-type psoriasis. Generalized psoriasis, erythroderma, palmoplantar psoriasis, generalized pustular psoriasis, scalp and nail psoriasis, psoriasiform dermatitis and psoriatic arthropathy all have been reported in association with lithium therapy.^{6,34} The clinical features and histopathology of lithium-related psoriasis do not differ considerably from those of idiopathic psoriasis.³⁵

Pathogenesis

Different mechanisms have been involved in the pathogenesis of lithium induced psoriasis. It has been suggested that lithium may influence the pathogenesis of psoriasis at both molecular and cellular level.³⁶

A) Pathogenesis at molecular level

- Adenyl cyclase system hypothesis- In the past, researchers theorized that the decrease in cAMP from lithium treatment caused low intracellular levels of calcium, leading to a lack of differentiation, increased proliferation of keratinocytes, and enhanced chemotaxis and phagocytic activity of polymorphonuclear leukocytes. But studies showed that the short-term use of lithium leads to diminution of intracellular cAMP, but long-term lithium treatment causes just the opposite response through a compensatory mechanism.^{3,37}
- Inositol depletion hypothesis- Proposed mechanisms is the decreased levels of inositol in the skin may lead to the triggering or the exacerbation of psoriasis. Inositol is a component of the intracellular second messenger system linked to various neurotransmitters effecting cell function, growth, and differentiation. The pathway is dependent on the phosphatidyl inositol 3,4-diphosphate (PIP2). Receptor-activated phospholipase C hydrolyzes PIP2 in the cell membrane to inositol phosphate 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 induces the release of calcium from intracellular stores and DAG activates protein kinase C. An important source for the recycling of inositol to form PIP2 is the hydrolysis of inositol monophosphate to inositol and inorganic phosphate. This reaction, catalyzed by the enzyme monophosphatase, is inhibited by therapeutic doses of lithium. By blocking this recycling reaction, the PIP2 form of inositol is depleted and the intracellular signaling pathway described above is concomitantly blocked.^{31-36,38}

B) Pathogenesis at cellular level-

- Recent studies established that lithium affects the 'psoriatic cytokine network' by triggering the secretion of TNF- α , interleukin-2, interleukin-6, and interferon- γ . The dysregulation in the production of these cytokines has been linked to the induction of psoriatic lesions.^{6, 38, 39}

Antimalarials

The synthetic oral antimalarial (AM) agents have been used in the prophylaxis and treatment of malaria and several dermatological disorders for many years. The most commonly used oral AMs are chloroquine and hydroxychloroquine.³⁸ At least three indications for the use of antimalarials in patient with psoriasis have been reported. These are psoriatic arthropathy, coexistent lupus erythematosus (LE) and antimalarial prophylaxis for travel to an endemic area.⁷ The exacerbation and induction of psoriasis during treatment with AMs has been widely acknowledged.⁴ It is estimated that up to 31 percent of patient with psoriasis would develop an exacerbation of their disease following antimalarial therapy.⁴⁰ The use of chloroquine and hydroxychloroquine in patients with psoriasis is considered by some to be a contraindication.⁴

Clinical features

1. Latency periods- Psoriatic skin lesions most often occur with a latency of 2 to 12 weeks (average of 3 weeks) after starting AMs. Longer latency period of about 40.5 weeks, especially in cases of pustular eruptions.⁴
2. Clinical form of psoriasis eruption caused by antimalarials- Most common is the aggravation of preexisting psoriasis. Induction of pustular eruption may occur in preexisting psoriasis but de novo pustular psoriasis is uncommon.^{4, 7, 41, 42}

Pathogenesis

The chemical structure of the antimalarial drugs is very similar to that of dansylputrescine, a potent transglutaminase inhibitor. Transglutaminase is involved in the pathogenetic epidermal proliferation of psoriasis. Therefore antimalarial drugs probably trigger psoriasis through changes in the activity of the enzyme transglutaminase.⁴³

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a class of medications used for treatment of pain and arthritides. NSAIDs are frequently used by patients who have psoriasis as well as psoriatic arthritis. The evidence that NSAIDs exacerbate or induce psoriasis is not strong.⁷ Nevertheless, in some patients, exacerbation of psoriasis and arthritis may coincidentally occur simultaneously with the use of NSAIDs. Naproxen was the most common culprit in one study⁴⁴.

Indomethacin, both topical and oral indomethacin is found to associated with exacerbation of psoriasis.^{45,46} Generalized pustular psoriasis developed in a patient with phenylbutazone.⁴⁷ The experience of many dermatologists does not suggest that NSAIDs have any obvious adverse effect on psoriasis. The effects of NSAIDs have a short latency period, 1.6 weeks on average without significant variations between the different subsets of drug-provoked psoriasis⁴.

Pathogenesis

NSAIDs inhibit the metabolism of arachidonic acid by the cyclooxygenase pathway, leading to an accumulation of leukotrienes, which have been postulated to aggravate psoriasis. Elevated levels of these inflammatory mediators in psoriatic skin were found or indirectly confirmed in a number of studies.⁴⁸

Antibiotics

The influence of antibacterials on the course of psoriasis is controversial. The antibiotics that have been implicated in psoriasis are tetracyclines, including doxycycline, penicillin, amoxicillin and ampicillin^{49,50}. In one study, investigators reported that 4.11 percent of patients experienced exacerbation of psoriasis as a consequence of tetracycline use⁴. It has also been suggested that tetracyclines should be avoided in patients with clinical evidence of psoriasis, as well as in healthy individuals with a genetic predisposition for psoriasis. Macrolides and penicillin derivatives were associated with psoriasis in one multivariate case-control model in patients less than 50 years of age.⁴⁹ Reports suggest that exacerbation of psoriasis by penicillin derivatives is rare and may actually represent acute generalized exanthematous pustulosis and not true drug-provoked psoriasis.^{50, 51}

Clinical features- There has been no detailed study on the latency period of tetracyclines. Antibiotics may be associated with onset or exacerbation of already existing psoriasis.⁴

Pathogenesis- Tetracyclines provoke psoriasis probably via the reduction of intracellular cAMP or by the interaction of the drug with arachidonic acid and its metabolites. Tetracyclines accumulate in higher concentrations in psoriatic lesions than in clinically uninvolved skin. It is well established that they are photosensitizing agents. Predisposed and psoriatic patients may undergo a Koebner phenomenon as a result of the photosensitizing properties of tetracyclines.^{3, 52, 53}

Diagnosis of drug related psoriasis

There are 5 important points for the diagnosis

- Detailed history of when drug treatment started, dosage regimen, and therapy duration
- Absence of additional triggering factors (stress, trauma, infections)
- Clinical relationship between the introduction of the drug and the onset of cutaneous manifestation
- Withdrawal of the drug followed by improvement of dermatologic status
- Histologic findings. Average values of the various histologic parameters (hyperkeratosis, parakeratosis, hypogranulosis, acanthosis, spongiosis, edema, and infiltration) measured for both drug-related psoriasis and controls with early eruptive psoriasis showed statistically significant differences for hyperkeratosis in the control group ($p < 0.05$) and spongiosis in the drug-related psoriasis group ($p < 0.05$).⁴

Guideline for the management of drug-related psoriasis

Management of drug-provoked psoriasis includes detailed personal, social, and family history. The absence of additional triggering factors should always be ruled out first. Patients should be encouraged to avoid alcohol, excessive sun exposure, smoking, stress and other factors that can all affect the clinical course of the disease. The distinction between drug-induced and drug-triggered psoriasis is of crucial importance for appropriate management. In case of drug induced psoriasis withdrawal of the implicated drug is followed by clinical improvement and can be managed with emollients alone. Management of drug-triggered psoriasis is difficult and required full range of topical and systemic modalities of treatment of idiopathic psoriasis⁴.

Treatment of β -blockers induced or provoked psoriasis-

Cardiologists may underestimate the fact that β -blockers worsen the course of psoriasis. Consultation by a dermatologist is advisable in such cases for the benefit of the patient. Psoriasiform eruptions regress rapidly after discontinuation of the drug. Exacerbation of psoriasis by β -blockers is resistant to treatment unless the drugs are discontinued⁴. If psoriasis is present only in localized areas, emollients alone can be helpful.

Unresponsive cases of drug provoked psoriasis needs use of conventional therapeutic agents that include topical and systemic agents used in the treatment of psoriasis vulgaris³. Hospitalization is required for beta-blocker induced erythroderma to monitor hypovolemia and hemodynamic instability, aggressive fluid resuscitation. Aggressive treatment with systemic and topical agents in concordance with discontinuation of the offending drug is also necessary^{3,4}.

Treatment of Lithium-induced or -exacerbated psoriasis-

Many therapeutic modalities have been used with variable success, and conventional topical treatment has become less effective as lithium-induced or -exacerbated psoriasis is often recalcitrant to treatment.^{4,32, 54} Discontinuation of lithium results in disappearance of the lesions within 6 months but skin changes are reversible, and most often readministration of lithium is followed by a rebound flare.^{36, 54}

Inositol supplementation in diet- Peripheral inositols received in the form of dietary consumption do not cross the blood-brain barrier and therefore do not alter lithium effects on mood stabilization. Significant improvement after 6g of daily inositol supplementation by mouth is noticed with “dramatic improvement” within 48 to 72 hours.⁵⁵

In some cases, patients can develop treatment-resistant psoriasis, which may warrant discontinuation of lithium with change to another mood-stabilizing agent depending on the severity of cutaneous involvement. Reduction in dosage of lithium is an additional option for treatment-resistant cases.⁵⁴ TNF- α inhibitors, such as etanercept, in the treatment of severe, recalcitrant, lithium-provoked psoriasis.⁵⁶

Treatment of Antimalarial and tetracycline induced psoriasis-

Resolution of psoriatic lesions usually occurs within one month of discontinuing the AM agent.

Tetracyclines should be avoided in patients with clinical evidence of psoriasis as well as in healthy persons with genetic predisposition for psoriasis^{4, 38}.

Conclusion:

Several drugs have been associated with drug-provoked psoriasis. Why provocation of psoriasis occurs in some individuals and not others who are exposed to a specific

drug remains unclear. Understanding the pathogenesis of drug-provoked psoriasis not only helps to achieve a greater appreciation of the disease process, but is also useful in providing guideline for treatment methodologies. Drugs that are considered to have a strong potential risk factor for psoriasis development should be avoided after weighing the risk and benefits of the agent. Fortunately, there are only a few drugs that demonstrate a well-documented, direct, causal relationship with the development of psoriasis or psoriasiform eruptions, and alternative therapeutic options are frequently available.

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