

Review

Lithium and Psoriasis

Yalçın Tüzün, MD, Gürkan Yardımcı,* MD

Address: Department of Dermatology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey

E-mail: yalcintuzun@yahoo.com

* Corresponding Author: Dr. Gürkan Yardımcı, Department of Dermatology, Cerrahpaşa Medical Faculty, Istanbul University, Fatih, Istanbul, 34098, Turkey

Published:

J Turk Acad Dermatol 2009; 3 (4): 93401r

This article is available from: <http://www.jtad.org/2009/4/jtad93401r.pdf>

Key Words: psoriasis, lithium

Abstract

Background: Psoriasis is a chronic multifactorial inflammatory disease which affects 0.1-3% of the global population. Some factors may induce or aggravate psoriasis and one of these factors is lithium. The mechanism of lithium-related psoriasis is exactly unknown. Various clinical types of psoriasis can be seen and most of the cases are resistant to classical treatments.

Psoriasis is a chronic multifactorial inflammatory disease which affects 0.1-3% of the global population [1]. This disease has a significant impact on the patient's quality of life. Psoriasis is characterized by T cell-mediated hyperproliferation of keratinocytes and inflammatory responses. Naive T cells are transformed to T cells of the Th1 and Th2 lineages in secondary lymphatic organs, which produce cytokines such as IL-22, IFN- γ , TNF- β and IL-6, IL-17, consequently. Those immune cells infiltrate the skin and activate each other and the keratinocytes via the previously mentioned cytokines and additional ones (such as TNF- α , IL-20, IL-23, TGF- α), which gives rise to an inflammatory process [2].

A variety of potential risks or triggering factors have been described such as smoking, alcohol consumption, body mass index (BMI), trauma, infections, stressful life, endocrine factors, diet, or medications. Many drugs including β -blockers, lithium, and antimalarials have been associated with psoriasis, but there have also been reports for NSAIDs, angiotensin-converting enzyme inhibitors, interferons, SSRIs, benzodiazepines, and the

immediate withdrawal of systemic or potent topical corticosteroids [2].

The name lithium was derived from the Greek word *lithos*, meaning stone. Lithium was first discovered as an element by Johan August Arfvedson in 1817. Lithium's use in modern medicine dates back to the mid-19th century. Use of lithium was approved by the US FDA in 1970 for the treatment of acute mania and in 1974 for the maintenance therapy and prophylaxis of patients with bipolar disorder [3]. This drug is used in psychiatry in the form of lithium carbonate and lithium citrate mainly for the treatment and prophylaxis of some disorders, such as mania and manic-depressive syndrome [4]. Nevertheless, lithium's toxicity limits its use [5]. Ordinary blood-plasma levels of lithium's concentration are 0.6-1.2 mEq/L, which has very narrow therapeutic range [4]. Plasma concentrations exceeding 1.5 mEq/L result in multisystemic adverse reactions, such as central nervous system, kidneys, thyroid gland, gastrointestinal tract and skin [4, 6]. The prevalence of cutaneous side effects in patients use lithium ranges from 3.4% to 45% [7]. Cutaneous ad-

verse effects were first described in 1968 by Callaway et al who reported 5 cases of lithium induced skin eruption [8, 9]. Side effects on the skin include acneiform and maculopapular eruptions, alopecia, and induction and exacerbation of psoriasis [10]. A causal relationship between psoriasis and lithium compounds was doubted in 1972. Lithium-provoked psoriasis was first reported in 1976 [1].

The mechanism of lithium-induced psoriasis is not completely understood and possible mechanisms include:

- Disruption of ion transport system leading to reduced cyclic adenosine monophosphate (cAMP) and inositol levels
- Dysregulation of the cytokine network (e.g. affecting levels of interferon- α and interleukin-2 in skin from patients with psoriasis)
- Stimulation of neutrophil production by blocking the inhibitory effects of prostaglandin (modulated by reduced cAMP)
- Increase in circulating neutrophil levels and promotion of lysosomal release from leukocytes [1, 7].

Several mechanisms have been involved in the pathogenesis of lithium-induced psoriasis. They have been divided into two groups:

1. Mechanisms acting on the molecular level
2. Mechanisms acting on the cellular level [4, 11].

At the cellular level lithium has mitogen properties and acts by blocking cell differentiation [6]. Effects on chemotaxis may support division of the exacerbation or induction of psoriasis, especially in its pustular variants [4]. This drug increases the total mass of neutrophils and speeds up their turnover and migration to experimentally induced skin lesions [6]. Pertinent immunologic effects of lithium may include increased lymphocyte reply to mitogens, possibly modulated by T-suppressor cells, and changed lymphokine production [4].

On the molecular level, assumed mechanism of lithium-exacerbated psoriasis includes cAMP-mediated courses [4, 12]. Lithium influences cAMP levels. A short term use of lithium leads to decrease of intracellular cAMP. Unlike to this, a long term use of lithium, by a homeostatic compensatory mechanism, increases intracellular levels of cAMP. Because of these contradictions it suggests that lit-

hium-induced psoriasis is probably not directly related to an interference with the adenylyl cyclase system [6]. Also decreased cAMP is included in the inhibition of prostaglandin synthesis and thus stimulating neutrophil proliferation [3, 13].

Lithium may also affect protein kinase C-inositol biphosphate pathway through inhibition of inositol-1-phosphatase and this may result alteration of the cellular transduction signals [4, 6]. Inositol is a component of the intracellular second messenger system linked to various neurotransmitters affecting cell function, growth, and differentiation. This pathway is necessary for the release of intracellular calcium, which in the skin is important in keratinocyte proliferation and differentiation [10]. Lithium has inhibitory effects on signal-transducing G-proteins and the phosphatidylinositol system, resulting decreased of cAMP and inositol levels [5]. The decrease in cAMP and inositol by lithium causes low calcium levels on the cell, leading to lack of differentiation and increased proliferation of keratinocytes, improved chemotaxis, and phagocytic activity of leukocytes [3, 5, 14]. Inositol supplementation in psoriatic patients on lithium treatment has showed benefits [3, 15, 16].

Recent studies suggest that IL-6 and its inducer TNF may play an important role in the pathogenesis of psoriasis [4]. The participation of endogenous TNF and IL-6 may have triggered or aggravated psoriasis in lithium-treated patients in a murine model [4, 17]. Ockenfels et al showed that lithium effects the cellular communications of psoriatic keratinocytes when cultured with HUT-78 lymphocytes by triggering the secretion of TGF- α , INF- γ , and IL-2 levels in the skin of patients with psoriasis after lithium treatment [3, 18].

In vitro studies of culture of normal human skin with lithium have demonstrated lithium's direct role in epidermal hyperproliferation, and indirect role in altering epidermal barrier function and generating signals to the nucleated layer of the epidermis to proliferate in an attempt to restore the barrier, increasing cell turnover, intercellular edema, and vacuolar alteration with formation of small cavities in the upper dermis [3, 19].

Lastly some authors have described that lithium increased intracellular tyrosine phospho-

horylation in psoriatic T cells compared to control T cells and may have important role in the pathogenesis of psoriasis [3, 10, 20].

Lithium has been described to induce biochemical alteration in keratinocytes and T cells, in this way it may induce or exacerbate psoriasis in genetically predisposed persons [10].

There is a latent period between lithium treatment and appearance de novo psoriasis or aggravate preexisting psoriasis [4]. Latency periods are classified as follows:

- short: less than 4 weeks
- intermediate: 4 to 12 weeks
- long: more than 12 weeks [6].

Typically the latency period of the de novo psoriasis is longer than exacerbation of preexisting psoriasis. This period is considerably variable and may be a few weeks to a several months [3]. This period was of average duration 33.3 ± 6.2 weeks and might be categorized as 'long'. Exacerbation of preexisting psoriasis was more frequent than provocation *de novo*, and the latent period was shorter [4, 11].

Psoriasis is the most common side effect on the skin and it is not always dose-related [10]. Lithium may induce de novo psoriasis or aggravate preexisting psoriasis [1]. The most common form of lithium-induced psoriasis is frequently on the scalp, which has clinical signs as widespread psoriatic plaques and resistant to the conventional treatments [5]. But pustular psoriasis, fingernail abnormalities, erythroderma, nonspecific psoriasisiform dermatitis, and psoriatic arthropathy may also appear [3]. The clinical manifestation of psoriasis, which is induced or exacerbated by lithium, did not seem to differ from idiopathic psoriasis [4]. The clinical and histopathologic signs of lithium-induced psoriasis are compatible with idiopathic psoriasis and there are no specific histopathologic differences [3]. About half of the cases reported a positive family history was available, the other one-half of cases had new onset psoriasis [5]. Rough and yellowish colored nails with opacity or pitting have been reported in some cases who have received lithium treatment [3]. In a study, these lesions were shown to be reversible after discontinuation lithium treatment [3, 21]. Erythroderma or exfoliative dermatitis secondary to lithium treatment is relatively rare [3, 4]. In these rare manifesta-

tions, psoriatic lesions may spread to various sites of the body such as scalp, trunk, and extremities. Discontinuation of lithium has been proven to be useful in improvement of the condition [3]. Lithium-induced psoriasis has been reported to progress to psoriatic arthritis [3, 22].

Lithium-induced or aggravated psoriasis is resistant to classical treatment [4, 6]. In these cases topical steroids, keratolytics, vitamin D analogues, oral retinoids, PUVA (psoralen and ultraviolet A), and methotrexate can be used [3, 5]. But in many cases these treatments are not effective [3, 4]. Lithium treatment may be stopped and replaced by another behaviour stabilizer in refractory cases. Tapering the dose should also be considered as an alternative treatment option [3]. Psoriatic lesions usually disappear within 6 months after discontinuation lithium treatment. [2, 4, 6]. But in most cases skin changes are reversible and following re-use of lithium rebound attacks can be seen. This effect proves that lithium has a role in the development of psoriatic lesions [4, 6]. Several new therapeutic agents such as omega-3 fatty acids, tumor necrosis factor (TNF)- α inhibitors, and inositol can be used in the treatment lithium-induced psoriasis but not used in routine [3]. In a double-blind, placebo controlled trial, omega-3 fatty acids was found to be very useful in healing lithium-induced psoriasis [3, 23]. Some authors have successfully used TNF-inhibitors (etanercept) in the treatment severe resistant lithium-induced psoriasis nonresponsive to other treatment alternatives [3, 24]. In a randomized, double-blind, placebo controlled crossover trial, inositol supplementation was found to have beneficial effects on psoriasis in patients who were taking lithium compared to those who were not taking lithium [3, 16]. The beneficial effect of inositol is related to lithium's 'inositol depletion hypothesis' in the pathogenesis of lithium-induced psoriasis. **Table 1** summarizes the management guidelines for lithium-induced production or exacerbation of psoriasis [3].

References

1. Dika E, Varotti C, Bardazzi F, Maibach HI. Drug-induced psoriasis: an evidence-based overview and the introduction of psoriatic drug eruption probability score. *Ocul Toxicol* 2006; 25: 1-11. PMID: 16702050

Table 1. Management Guidelines for Lithium-Induced Production or Exacerbation of Psoriasis [3]

Detailed personal, social, and family history and history of psoriasis before considering lithium therapy
Psychodermatologic evaluations at frequent intervals during the treatment course to recognize psoriatic lesions and address potential issues with low self-esteem and treatment compliance
Mild to moderate disease: conventional treatment such as topical steroids, vitamin D analogues, retinoids, methotrexate, and PUVA (psoralen and ultraviolet A) therapy
Severe disease: discontinue lithium treatment and request dermatology/psychodermatology consult. Reduction of dose could be another option reasonable and worth trying in these cases
Consistent liaison among primary care physician, psychiatrist, and dermatologist regarding the management of psoriasis
Patient and family education regarding the association of lithium and psoriasis and provision of alternative medications

2. Brauchli YB, Jick SS, Curtin F, Meier CR. Lithium, antipsychotics, and risk of psoriasis. *J Clin Psychopharmacol* 2009; 29: 134-140. PMID: 19512974
3. Jafferany M. Lithium and psoriasis: what primary care and family physicians should know. *Prim Care Companion J Clin Psychiatry* 2008; 10: 435-439. PMID: 19287551
4. Tsankov N, Kazandjieva J, Drenovska K. Drugs in exacerbation and provocation of psoriasis. *Clin Dermatol* 1998;16: 333-351. PMID: 9642528
5. Yeung CK, Chan HH. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol* 2004; 5: 3-8. PMID: 14979738
6. Tsankov N, Angelova I, Kazandjieva J. Drug-induced psoriasis. Recognition and management. *Am J Clin Dermatol*. 2000; 1: 159-165. PMID: 11702297
7. Long-term lithium therapy is associated with skin reactions - predominantly acne and psoriasis. *Drugs Ther Perspect* 2005; 21: 22-25.
8. Chan HH, Wing Y, Su R, Van Krevel C, Lee S. A control study of the cutaneous side effects of chronic lithium therapy. *J Affect Disord* 2000; 57: 107-13. PMID: 10708822
9. Callaway CL, Hendrie HC, Luby ED. Cutaneous conditions observed in patients during treatment with lithium. *Am J Psychiatry*. 1968; 124: 1124-1125. PMID: 5638076
10. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. *Clin Dermatol* 2007; 25: 606-615. PMID: 18021899
11. Tsankov N, Kazandjieva J, Drenovska K. Drugs in exacerbation and provocation of psoriasis. *Clin Dermatol* 1998;16: 333-351. PMID: 9642528
12. Voorhees JJ, Duell EA. Psoriasis as a possible defect of the adenylyl cyclase-cyclic AMP cascade; a defective chalone mechanism? *Arch Dermatol* 1971; 104: 352-358. PMID: 4329804
13. Rothstein G, Clarkson DR, Larsen W, Grosser BI, Athens JW. Effect of lithium on neutrophil mass and production. *N Engl J Med* 1978; 26: 298: 178-180. PMID: 619259
14. Voorhees JJ, Marcelo CL, Duell EA. Cyclic AMP, cyclic GMP and glucocorticoids as potential metabolic regulators of epidermal proliferation and differentiation. *J Invest Dermatol* 1975; 65: 179-190. PMID: 168273
15. Grisaru N, Belmaker RH. Lithium dosage and inositol levels. *Br J Psychiatry* 1994; 164: 133-134. PMID: 8137104
16. Allan SJ, Kavanagh GM, Herd RM, Savin JA. The effect of inositol supplements on the psoriasis of the patients taking lithium: a randomized placebo-controlled trial. *Br J Dermatol* 2004; 150: 966-969. PMID: 15149510
17. Beyaert R, Schulze-Osthoff K, Van Roy F. Synergic induction of interleukin-6 by tumor necrosis factor and lithium chloride in mice: Possible role in the triggering and exacerbation of psoriasis by lithium treatment. *Eur J Immunol* 1992; 22: 2181-2184. PMID: 1322305
18. Ockenfels HM, Wagner SN, Keim-Maas C, Funk R, Nussbaum G, Goos M. Lithium and psoriasis: cytokine modulation of cultured lymphocytes and psoriatic keratinocytes by lithium. *Arch Dermatol Res*. 1996; 288: 173-178. PMID: 8967788
19. Wolf R, D'Avino M, De Angelis F, Ruocco E, Lombardi ML. Effects of lithium carbonate (LiCO₃) on in-vitro cultured normal human skin explants. *J Eur Acad Dermatol Venereol* 2000; 14: 97-99. PMID: 10972093
20. Ockenfels HM, Nussbaum G, Schultewolter T, Mertins K, Wagner SN, Goos M. Tyrosine phosphorylation in psoriasis T cells in modified by drugs that induce or improve psoriasis. *Dermatology* 1995; 191: 217-225. PMID: 8534940
21. Rudolph RI. Lithium-induced psoriasis of the fingernails. *J Am Acad Dermatol* 1992; 26: 135-136. PMID: 1732326
22. Skerritt PW. Psoriatic arthritis during lithium therapy. *Aust N Z J Psychiatry* 1987; 21: 601-604. PMID: 3130043
23. Akkerhuis GW, Nolen WA. Lithium-associated psoriasis and omega-3 fatty acids. *Am J Psychiatry* 2003; 160: 1355. PMID: 12832259
24. Wachter T, Murach WM, Bröcker EB, Schön MP. Recalcitrant lithium-induced psoriasis in a suicidal patient alleviated by tumour necrosis factor-alpha inhibition. *Br J Dermatol* 2007; 157: 627-629. PMID: 17596151