

A Review of Drugs That Induce or Exacerbate Psoriasis

Julie Hong,¹ Daniel Bernstein, BS²

ABSTRACT

Background: Psoriasis is a common disorder of the skin, immune system, and joints that is influenced by genetic and environmental factors. It can be aggravated or induced by drugs.

Objectives: To identify the major drugs implicated in inducing or exacerbating psoriasis and to discuss their characteristics.

Methods: We performed a PubMed literature search for reviews and case reports on drugs that exacerbate or induce psoriasis. Articles were screened by title and abstract and then examined for their findings and references.

Results: Drugs most often reported to exacerbate or induce psoriasis were β -blockers, lithium, synthetic antimalarials, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, interferons, tetracyclines, tumor necrosis factor- α inhibitors, and steroid withdrawal.

Conclusions: Characterizing drugs that induce or exacerbate psoriasis by latency and type of psoriatic eruption can help guide clinical reasoning. Although a relatively uncommon occurrence, psoriatic lesions can be caused by drugs, allowing astute physicians to recognize and change their management plans accordingly.

INTRODUCTION

Psoriasis is a chronic systemic, inflammatory disease that is manifested in the skin, nails, and joints. Although psoriasis is currently thought of as a disorder of the immune system, many environmental factors can affect the type and location of specific lesions. Of the several known triggers for psoriasis, drugs can exacerbate psoriasis even after long latency periods.

This article focuses on several drugs associated with worsening or development of psoriasis. Those drugs most widely accepted as offenders are β -blockers, lithium, synthetic antimalarials, tetracyclines, and nonsteroidal anti-inflammatory drugs (NSAIDs); withdrawal from systemic corticosteroids can also be a trigger. Other drugs commonly reported to worsen or induce psoriasis include, but are not limited to, interferons, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor

¹Mount Sinai School of Medicine, New York, New York; ²Albany Medical College, Albany, New York

Corresponding author

Daniel Bernstein, BS
1125 Crescent Dr.
Tarrytown, NY 10591
Tel: 315.254.7454
E-mail: bernstd@mail.amc.edu

Disclosures

The authors have no conflicts of interest to declare.

Key words: psoriasis, drug, medication, induction, exacerbation, review

blockers, terbinafine, tumor necrosis factor (TNF)- α , and gemfibrozil.

Drugs can induce psoriasis de novo or induce lesions in previously unaffected skin and can exacerbate psoriasis in a patient already afflicted with psoriasis by causing flares or treatment resistance.¹ In addition, any drug eruption in a patient with psoriasis may provoke widespread psoriasis in its wake.² This review focuses on the latency period between drug administration and psoriatic eruption and the type of psoriatic eruptions seen (Table 1) and includes a discussion of the proposed mechanisms by which the drugs exert their effects.

Table 1. Latency Periods as Described by Tsankov et al³

Latency	Drugs
<4 Wk = short	Nonsteroidal anti-inflammatory drugs
4-12 Wk = intermediate	Synthetic antimalarials
>12 Wk	Lithium
Variable	β -blockers

METHODS

A review of the literature on drug-induced and drug-exacerbated psoriasis was conducted using PubMed. The search was limited to articles published from 1965 to present, with abstracts in English about humans, and included meta-analyses, randomized controlled trials, reviews, and case reports.

Titles were searched for key words using the following combinations: [(*psoriasis* or *psoriatic* or *psoriasiform*) with (*exacerbation* or *exacerbated* or *induction* or *induced* or *drug* or *medication*)] or [(*psoriasis* or *psoriatic*) with (*NSAIDs* or *antimalarials* or *angiotensin-converting enzyme* or *sartans* or *interferon* or *β -blocker* or *lithium* or *corticosteroid withdrawal* or *steroid withdrawal* or *terbinafine* or *tetracycline* or *anti-TNF* or *gemfibrozil*)].

In total, 205 articles met these criteria and were further screened by abstract for relevance to our topic, resulting in 89 relevant articles. We assessed each of the 89 remaining articles for the type of study, type of psoriatic eruption, the implicated drug, and the latency period before the eruption. In addition, the sources cited in any of these 89 articles were

examined to present a more in-depth review of the subject material.

RESULTS

Of the 89 articles that met inclusion criteria, there were no meta-analyses or randomized controlled trials, 11 were reviews, and 72 were case reports. Six articles were both case reports and reviews. Of the articles meeting the inclusion criteria on induction or exacerbation of psoriasis by a drug, 24 (27%) pertained to TNF- α inhibitors and 16 (18%) were on interferons (Table 2).

Table 2. Results of Literature Search

Article Focus	No. of Articles
Tumor necrosis factor-alpha (TNF- α) inhibitors	24
Interferons	16
Non-TNF biologics	5
β -blockers	4
Lithium	4
Angiotensin-converting enzyme inhibitors	4
Synthetic antimalarials	3
Granulocyte colony-stimulating factor	2
Terbinafine	2
Anticonvulsants	2
Antidepressants	2
Steroids	1
Cyclosporine	1
Testosterone/estrogens	1
Imiquimod	1
Penicillin	1
Calcium-channel blockers	1
Other	15

DRUGS INDUCING OR EXACERBATING PSORIASIS

β -Blockers

There are numerous reports of β -blockers inducing and exacerbating psoriasis,⁴ at times causing psoriasis vulgaris to become pustular⁵ or erythrodermic.³ β -2 receptors are found in keratinocytes, which can lead to decreased cyclic adenosine monophosphate (cAMP) and consequent increases in intracellular calcium, causing increased cell proliferation with decreased differentiation.^{1,6,7} The latency period between drug exposure and psoriatic eruption can

vary significantly, from several days to 48 weeks; if eruptions are indeed found, they are usually resistant to antipsoriatic medications until the β -blocker is discontinued.⁴

Probably every β -blocker is capable of provoking psoriasiform eruptions, aggravation, or induction of the condition,⁶ including but not limited to the β -blockers propranolol,⁸⁻¹⁰ oxprenolol,^{6,11,12} practolol,^{11,13-15} metoprolol,^{9,16} atenolol,^{5,9} cetamolol,¹⁷ timolol,¹⁸ and nadolol.⁹ Therefore, merely substituting one β -blocker for another may be unwise.¹¹

For patients with psoriasis, β -blocker therapy is a particularly important issue. Recent evidence has shown an association between psoriasis and increased endothelial dysfunction and oxidative stress.¹⁹⁻²¹ Thus, the contraindication to β -blockers for these patients is only relative in the presence of absolutely indicated cardiac situations.²² Many patients with psoriasis are managed effectively despite treatment with β -blockers.

Lithium

Lithium is reported to cause cutaneous side effects in up to 45% of patients; these adverse effects can include acneiform eruptions, psoriasis, folliculitis, and maculopapular eruptions.²³ Interestingly, male patients may have a greater risk of a cutaneous side effect than do female patients.²³ The mechanisms proposed include alteration to intracellular calcium homeostasis via cAMP levels and the inositol triphosphate pathway.^{4,24,25} There are also hypotheses that lithium is acting as a direct mitogen,⁴ as well as inducing the release of proinflammatory cytokines like interleukin-2 (IL-2), IL-6, and interferon- γ .²⁶ Reactions include, but are not limited to, plaque psoriasis,^{27,28} palmoplantar psoriasis,²⁴ pustular psoriasis,^{24,29} scalp psoriasis,²⁸ erythroderma,²⁸ nail changes,³⁰ and psoriatic arthritis.³¹ The latency period for induction can take up to 48 weeks, although shorter latency has been noted with exacerbations at an average at about 20 weeks.⁴

Lithium is a commonly prescribed drug for psychiatric disorders as well as for uric acid. However, lithium has not been reported to induce psoriatic eruptions in urology practice, perhaps because the course of lithium in these patients is markedly shorter.⁶ Unfortunately, psychiatric patients have a direct

relationship between the emergence of psoriatic eruptions and therapeutic relief from their manic symptoms.³² Other drugs taken concomitantly, like carbamazepine, may increase the risk of a psoriatic eruption.³³

Psoriasis also has strong effects on the mental health of patients, causing psychosocial morbidity and decreased occupational function.¹⁹ Even beyond prescriptions, one group of authorities found that water can be contaminated with enough lithium to be clinically relevant, suggesting that lithium-induced psoriasis should be kept in the differential diagnosis for any patient with acute-onset psoriasis that is resistant to therapy.³⁴

Synthetic Antimalarial Drugs

Antimalarials are implicated in the exacerbation of psoriasis, although they are rarely reported to induce psoriasis de novo.³⁵ Induction of psoriasis has been reported with many synthetic derivatives of quinine, and reviews of the literature have estimated that 31% of patients with psoriasis could have an antimalarial-related exacerbation of their condition.⁶

Inhibition of transglutaminase is one proposed mechanism. It causes decreased epidermal differentiation,³ whereas drugs that induce epidermal differentiation, such as vitamin D derivatives and retinoids, are known to induce transglutaminase.³⁵

An intermediate latency ranging from 3 to 40.5 weeks is reported, and a variety of psoriatic eruptions are described,³ including pustular eruptions and even onychoparonychia with the use of hydroxychloroquine.^{36,37} This is complicated by the fact that hydroxychloroquine may be better tolerated than chloroquine for patients with psoriatic arthritis, although both have been specifically used as therapy for psoriatic arthritis.^{1,38}

Even though antimalarials are used to treat psoriatic arthritis far less often than are NSAIDs, antimalarials have a much higher incidence of psoriatic eruptions.³⁵ This has resulted in some authorities considering antimalarials to be contraindicated in patients with psoriasis,^{3,6,39} although others disagree to varying degrees.⁴⁰⁻⁴⁴

Nonsteroidal Anti-inflammatory Drugs

The NSAIDs, which are among the most widely used medications in the world, have many known adverse effects. NSAIDs have been reported to exacerbate psoriasis and induce generalized pustular psoriasis,⁴⁵⁻⁴⁷ although some small studies have not found adverse effects with respect to psoriasis.^{48,49}

With a mechanism similar to those previously described, prostaglandin E₂ is hypothesized to dovetail with the adrenergic regulation of adenylyl cyclase in the skin.⁵⁰ Therefore, NSAIDs that block cyclooxygenase affect intracellular calcium levels through modulation of adenylyl cyclase and cAMP generation. There is also evidence that arachidonic acid is diverted to the production of excess leukotrienes, namely, leukotriene B₄ (LTB₄), resulting in psoriasis flares.^{6,51} In particular, when psoriatic patients are compared with normal controls, they have shown resistance to LTB₄,^{52,53} with psoriatic lesions exhibiting no response whatsoever to LTB₄.⁶ This finding is further supported by improvement of psoriasis with benoxaprofen, a known inhibitor of 5-lipoxygenase.⁵⁴

The short latency period of NSAIDs is only 1.6 weeks on average.³ Most studies have focused on indomethacin as the instigating agent, although there are reports of phenylbutazone,⁵⁵ ibuprofen,⁵⁶ and meclofenamate^{57,58} causing or exacerbating psoriatic lesions as well. Benefit from NSAIDs for patients with psoriatic arthritis is muddled by the risk of adverse cutaneous reactions, although the risk of such reactions is relatively low.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

The ACE inhibitors are a cause of cutaneous side effects in up to 58.3% of patients.⁶ Clinical manifestations include treatment-resistant forms of guttate psoriasis, plaque psoriasis, palmoplantar psoriasis, pustular psoriasis, and psoriasiform drug eruptions.⁶

The ACE inhibitors captopril,^{59,60} enalapril,⁶⁰ and ramipril⁶¹ have been reported to cause psoriatic eruptions. Although the current theory is that ACE inhibitors cause a rise in bradykinin, which causes psoriatic lesions, the recent report of candesartan-induced pustular psoriasis calls this mechanism into question.⁶² Still, the kinin-kallikrein system is

closely connected to the arachidonic acid system, and perturbations of either system seem to affect psoriasis. Substance P is also implicated as a player in psoriatic lesions, and ACE is known to be involved in its degradation.⁶³ There is an intermediate latency period ranging from 4.1 weeks to 8.4 weeks on average for psoriatic eruptions.⁶

Even more concerning, however, are the implications in treating cardiovascular disease in patients with psoriasis. Cardiovascular medications that can decrease mortality include β -blockers and ACE inhibitors, but both are known causes of psoriasis exacerbation and induction.

Interferons

Interferons (IFNs) are now used as therapies for a wide variety of disease processes. Between 1986 and 1996, 17 patients were reported to have psoriatic lesions either induced or exacerbated by IFN- α requiring discontinuation of IFN therapy for the eruption to subside; three similar cases were added in 1996,⁶⁴⁻⁶⁸ and additional cases were reported in 2000, 2005, and 2007.⁶⁹⁻⁷¹ IFN- α was also found to induce a seronegative arthritis in two patients.^{72,73}

IFN- β is reported to exacerbate psoriasis,⁷⁴ with one study showing concomitant induction of psoriatic arthritis during treatment for multiple sclerosis.⁷⁵ Once thought to be a potential new treatment for psoriatic arthritis, IFN- γ was even found to cause punctiform psoriatic foci at injection sites^{76,77} and did not provide long-term relief from arthropathy.^{67,74,76-78}

Although there are multiple mechanisms by which IFNs are thought to modulate psoriasis, it is clear that IFNs can alter cells of the immune system as well as keratinocytes.^{6,79} In particular, IFN- α therapy for patients with viral hepatitis should be carefully evaluated in patients with comorbid psoriasis.⁸⁰ A recent report even suggests the use of prophylactic etanercept (Enbrel) to inhibit potential psoriatic flares caused by IFN therapy,⁸¹ although most cases examined involve therapy for hepatitis C virus⁸¹⁻⁸³ or hepatitis B virus.⁸⁴

Latency between administration and psoriatic eruption was reported as being as little as 1 week.⁸⁵ Indeed, all forms of IFNs have been associated with the exacerbation of psoriatic plaques. Although only

IFN- α has induced psoriasis de novo, in theory at least, all forms of IFNs could induce de novo disease.⁷⁴

Steroid Withdrawal

Corticosteroids are a unique problem with psoriasis. Locally, and on a short-term basis, lesions regularly improve. However, generalized pustular psoriasis can result from withdrawal of corticosteroids in patients with psoriasis.⁸⁶ Whereas generalized pustular psoriasis is relatively uncommon, one study found that more than 33% of the cases examined were the direct result of steroid withdrawal.⁸⁷ It has therefore been proposed that systemic corticosteroids be contraindicated in psoriasis because of the risk of generalized pustular psoriasis, with new evidence suggesting that even potent topical steroids be avoided over large psoriatic skin areas because of the risk of systemic steroid absorption.^{1,86}

Nonetheless, steroids are required for many clinical situations in modern medicine, and it would be impractical to assume that patients afflicted with psoriasis can completely avoid systemic steroids over their life span. It is more realistic for physicians to familiarize themselves with the potential complications of giving systemic steroids to patients with psoriasis so that they can make the appropriate therapeutic decisions.

Other Agents

Tetracyclines

Tetracyclines are thought to exacerbate or induce psoriasis by a number of mechanisms, independent of infection.⁸⁸ Tetracyclines are known to decrease intracellular cAMP,⁸⁹ exert effects on the arachidonic acid system,⁹⁰ and photosensitize the skin, resulting in Koebnerization.

Tetracyclines have also been shown to localize in psoriatic lesions⁹¹ and are considered by some to be contraindicated in patients with psoriasis.^{88,92} Therefore, some authorities suggest that tetracyclines should be prescribed with caution in patients with latent or manifest psoriasis.⁹³ Conversely, several publications have shown therapeutic benefit of psoriasis from tetracyclines.⁹⁴⁻⁹⁶

Tumor necrosis factor- α inhibitors

The TNF- α inhibitors are relatively new drugs that are regularly used to treat psoriasis, psoriatic arthritis, and numerous other immunologic or rheumatic

diseases.⁴ Rarely, anti-TNF drugs can cause paradoxical exacerbation⁹⁷⁻⁹⁹ or even induction of psoriasis,^{92,100} requiring discontinuation of the drug. In a recent review of patients with psoriatic eruptions resulting from anti-TNF agents, 66% received infliximab (Remicade), 34% received etanercept, and 20% received adalimumab (Humira).⁹⁹ The prevalence of infliximab-related psoriatic eruptions is likely explained by infliximab being the main biological therapeutic used for longer than a decade, with adalimumab a far more recent addition to the therapeutic arsenal.¹⁰¹ Plaque psoriasis occurred slightly more often than did pustular psoriasis. Infliximab was linked to more cases of drug-related psoriasis than any other anti-TNF drug, most often between the third and fourth infusions.^{99,101} Many mechanisms have been hypothesized, including one that draws a connection between the blockade of TNF- α and a resultant enhancement of TNF- α activity with consequent induction of psoriasis.^{102,103}

Of the 24 articles found in our initial literature search, 16 case reports were detailed for further analysis (**Table 3**). A total of 52 cases were examined, with an average latency period of 38 weeks (excluding five cases where latency was given in terms of the number of infusions received) and a range of 4 days to almost 5 years. Thirty cases of psoriasis were attributable to infliximab (58%), 10 to etanercept (19%), and 12 to adalimumab (23%).

These data are similar to other reviews found in the literature. One study of 205 cases of anti-TNF-related psoriasis revealed 121 cases attributable to infliximab (59%), 40 to etanercept (20%), and 46 to adalimumab (22%).⁹² In addition, 110 cases exhibited pustular psoriatic lesions, and 98 showed plaque psoriasis.⁹² In contrast to publications about synthetic antimalarials that generally report psoriatic exacerbations, anti-TNF drugs caused new-onset psoriasis in 165 of the 205 reported cases.⁹² This last study did not examine latency periods.⁹²

One of the problems with adverse effects to anti-TNF drug therapy is that many patients do not begin a biologic therapy unless it is absolutely necessary. This means that patients often must tolerate adverse effects or run the risk of decompensation of their primary diagnosis. Still, new biologic therapies with new targets are being developed for psoriasis,¹¹⁶ holding much promise for the future. Biologic

Table 3. Case Reports of Anti-Tumor Necrosis Factor Agents Inducing or Exacerbating Psoriasis

First Author	Cases	Latency (wk)	Agent
Iborra et al ⁹⁸	1	2	Infliximab
Verea et al ¹⁰⁴	1	6	Infliximab
Alabed et al ¹⁰⁰	1	14	Infliximab
Manni and Barachini ¹⁰²	1	15	Infliximab
Pirard et al ¹⁰⁵	3	124	Infliximab
Takahashi et al ¹⁰⁶	4	28	Infliximab
Cohen et al ¹⁰⁷	5	74.2	Infliximab
	1	32	Etanercept
Cuchacovich et al ¹⁰⁸	4	30	Infliximab
	1	32	Adalimumab
Sfkakis et al ¹⁰⁹	3	29.3	Infliximab
	1	28	Etanercept
	1	36	Adalimumab
Wollina et al ¹¹⁰	3	104	Infliximab
	3	12.6	Adalimumab
Carter et al ¹¹¹	1	40	Infliximab
	1	12	Etanercept
	1	72	Adalimumab
Collamer et al ¹⁰³	1	100	Infliximab
	2	208	Etanercept
	1	52	Adalimumab
Kary et al ¹¹²	2	22	Infliximab
	3	5.3	Etanercept
	4	30.2	Adalimumab
Bovenschen et al ¹¹³	1	5	Etanercept
Sari et al ¹¹⁴	1	8	Etanercept
Borras-Blasco et al ¹¹⁵	1	5	Adalimumab

therapies are relatively new in medicine, and it is possible that new breakthroughs will further reduce the incidence of TNF- α inhibitor-induced psoriasis.

Terbinafine

Terbinafine is a commonly used antifungal that has been reported to exacerbate and induce psoriasis.⁶ Five cases are described in the literature, all resulting in either plaque or pustular psoriatic eruptions.^{117,118} The latency period for the eruptions ranged from 1.8 to 3.0 weeks, and all cases resolved with discontinuation of terbinafine.¹¹⁷

Because terbinafine has relatively specific indications, patients with psoriasis can avoid using the drug without much difficulty. Naturally, it has been proposed that oral terbinafine not be considered first-line therapy for superficial fungal infections in psoriasis patients.¹¹⁹ Nevertheless, dermatophyte infection is common in patients with psoriatic nail changes, and many psoriasis patients have been treated with terbinafine without worsening of their psoriasis.

Gemfibrozil

Gemfibrozil is one of many fibrate drugs used to modulate lipid profiles. Only two reports in the literature were of gemfibrozil causing a psoriatic eruption.^{120,121} There is no proposed mechanism by which gemfibrozil would cause a psoriatic eruption, and no other lipid-modulating agents have been shown to cause psoriatic lesions. However, systemically administered lipid-lowering drugs have been found to induce eczema and ichthyosis,¹²¹ revealing that cutaneous lesions are not uncommon with the use of lipid-lowering agents. The association between gemfibrozil and psoriasis should be viewed as anecdotal.

Notable drugs not frequently mentioned

Other drugs that do not appear in the literature in relation to inducing or exacerbating psoriasis include the following: penicillin, amoxicillin, ampicillin, morphine, procaine, cimetidine, ranitidine, gold, mercury, oxandrolone, progesterone, potassium iodide, granulocyte-macrophage colony-stimulating factor (GM-CSF)/granulocyte colony-stimulating factor (G-CSF), co-trimoxazole, clonidine, digoxin, amiodarone, quinidine, stazepin, valproate, carbamazepine, fluoxetine, bupropion, acetazolamide, imatinib, sorafenib, rituximab, and calcium-channel blockers.

CONCLUSIONS

Psoriatic eruptions resulting from use of certain drugs are relatively rare and are therefore difficult to study. Exacerbations of psoriasis are generally more common than inductions of new psoriasis.¹ Of all the various psoriatic lesions observed, plaque psoriasis is the most common.

Latency periods vary but were usually less than 2 weeks for NSAIDs,³ interferons,⁸⁵ and terbinafine.¹¹⁷ Intermediate latency periods were observed for synthetic antimalarials³ and ACE inhibitors.⁸ Longer latency periods, up to a year, were observed for β -blockers⁴ and lithium.⁴

It should be noted that it is often very difficult to distinguish clinically between a pustular drug eruption and drug-induced pustular psoriasis.¹²²⁻¹²⁵ Although biopsy and histologic examination can usually give a conclusive diagnosis, this is not always the case. At times, drug eruptions themselves can even cause an exacerbation of psoriasis, further confounding the clinical picture.^{2,124} Patch testing and lymphocyte stimulation tests may be useful.

It should also be noted that anti-TNF therapies have recently become some of the most commonly reported drugs to exacerbate or induce psoriasis. This is probably related to their recent emergence on the market and U.S. Food and Drug Administration approval for a number of chronic conditions. However, neither patients nor physicians need to become overly alarmed because, as of 2009, of 1.6 million patients who had used an anti-TNF agent,¹²⁶ only around 200 cases of psoriasis with anti-TNF therapy have been reported.⁹² Although uncommon, these reactions are still important to recognize and can help us understand more completely how psoriasis works on a molecular level. At the very least, more studies need to be done to characterize more fully psoriatic eruptions that occur as a result of biologic agents.

The most commonly effective therapy has been discontinuation of the implicated drug, although lesions tend to dissipate gradually over weeks to months. Some controversy remains over recommendations that certain drugs be contraindicated in patients with psoriasis, and such recommendations are not always practical. We are of the opinion that each clinical scenario must be appreciated in its appropriate context before therapeutic decisions can be made.

REFERENCES

1. Abel EA, DiCicco LM, Orenberg EK, Fraki JE, Farber EM. Drugs in exacerbation of psoriasis. *J Am Acad Dermatol.* 1986;15(5 Pt 1):1007-22.
2. Baker H. Psoriasis—clinical features. *Br Med J.* 1971;3(5768):231-3.
3. Tsankov N, Angelova I, Kazandjieva J. Drug-induced psoriasis: recognition and management. *Am J Clin Dermatol.* 2000;1(3):159-65.
4. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the Induction and/or exacerbation of psoriasis. *Int J Dermatol.* 2010;49(12):1351-61.
5. Wakefield PE, Berger TG, James WD. Atenolol-induced pustular psoriasis. *Arch Dermatol.* 1990;126(7):968-9.
6. Tsankov N, Kazandjieva J, Drenovska K. Drugs in exacerbation and provocation of psoriasis. *Clin Dermatol.* 1998;16(3):333-51.
7. Heng MC, Heng MK. Beta-adrenoceptor antagonist-induced psoriasiform eruption: clinical and pathogenetic aspects. *Int J Dermatol.* 1988;27(9):619-27.
8. Halevy S, Feuerman EJ. Psoriasiform eruption induced by propranolol. *Cutis.* 1979;24(1):95-8.
9. Gold MH, Holy AK, Roenigk HH Jr. Beta-blocking drugs and psoriasis. a review of cutaneous side effects and retrospective analysis of their effects on psoriasis. *J Am Acad Dermatol.* 1988;19(5 Pt 1):837-41.
10. Hu CH, Miller AC, Peppercorn R, Farber EM. Generalized pustular psoriasis provoked by propranolol. *Arch Dermatol.* 1985;121(10):1326-7.
11. Cumberbatch JB. Letter: skin reactions to beta-blockers. *Br Med J.* 1974;4(5943):528.
12. Macfarlane DG, Settas L. Acute psoriatic arthropathy precipitated by oxprenolol. *Ann Rheum Dis.* 1984;43(1):102-4.
13. Assem ES, Banks RA. Practolol-induced drug eruption. *Proc R Soc Med.* 1973;66(2):179-81.
14. Kauppinen K, Niemi KM, Salo OP. Cutaneous reactions to practolol: clinical and histopathological study. *Ann Clin Res.* 1976;8(4):232-40.
15. Sondergaard J, Wadskov S, Jensen HA, Mikkelsen HI. Aggravation of psoriasis and occurrence of psoriasiform cutaneous eruptions induced by practolol (Eraldin). *Acta Derm Venereol.* 1976;56(3):239-43.
16. Neumann HA, van Joost T. Adverse reactions of the skin to metoprolol and other beta-adrenoreceptor-blocking agents. *Dermatologica.* 1981;162(5):330-5.
17. White WB, Schulman P, McCabe EJ. Psoriasiform cutaneous eruptions induced by cetamolol hydrochloride. *Arch Dermatol.* 1986;122(8):857-8.
18. Puig L, Goni FJ, Roque AM, Bordas FD, de Moragas JM. Psoriasis induced by ophthalmic timolol preparations. *Am J Ophthalmol.* 1989;108(4):455-6.
19. Patel RV, Lebowitz M. In the clinic: psoriasis. *Ann Intern Med.* 2011;155(3):ITC2-1-15.
20. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol.* 2009;129(10):2411-8.
21. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. *Br J Dermatol.* 2008;159(4):895-902.
22. Yilmaz MB, Turhan H, Akin Y, Kisacik HL, Korkmaz S. Beta-blocker-induced psoriasis: a rare side effect—a case report. *Angiology.* 2002;53(6):737-9.
23. Yeung CK, Chan HH. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol.* 2004;5(1):3-8.
24. White SW. Palmoplantar pustular psoriasis provoked by lithium therapy. *J Am Acad Dermatol.* 1982;7(5):660-2.

25. O'Brien M, Koo J. The mechanism of lithium and beta-blocking agents in inducing and exacerbating psoriasis. *J Drugs Dermatol JDD*. 2006;5(5):426-32.
26. 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(4):173-8.
27. Bakker JB, Peppinkhuizen L. More about the relationship of lithium to psoriasis. *Psychosomatics*. 1976;17(3):143-6.
28. Skoven I, Thormann J. Lithium compound treatment and psoriasis. *Arch Dermatol*. 1979;115(10):1185-7.
29. Lowe NJ, Ridgway HB. Generalized pustular psoriasis precipitated by lithium carbonate. *Arch Dermatol*. 1978;114(12):1788-9.
30. Rudolph RI. Lithium-induced psoriasis of the fingernails. *J Am Acad Dermatol*. 1992;26(1):135-6.
31. Skerritt PW. Psoriatic arthritis during lithium therapy. *Aust N Z J Psychiatry*. 1987;21(4):601-4.
32. Carter TN. The relationship of lithium carbonate to psoriasis. *Psychosomatics*. 1972;13(5):325-7.
33. Sasaki T, Saito S, Aihara M, Ohsawa J, Ikezawa Z. Exacerbation of psoriasis during lithium treatment. *J Dermatol*. 1989;16(1):59-63.
34. Hanada K, Sawamura D, Sone K, Hashimoto I. Can lithium in spring water provoke psoriasis? *Lancet*. 1997;350(9090):1522.
35. Wolf R, Lo Schiavo A. Is transglutaminase the mediator between antimalarial drugs and psoriasis? *Int J Dermatol*. 1997;36(1):10-3.
36. Vine JE, Hymes SR, Warner NB, Cohen PR. Pustular psoriasis induced by hydroxychloroquine: a case report and review of the literature. *J Dermatol*. 1996;23(5):357-61.
37. Sibilia J, Cribier B, Javier RM, Pflumio F, Kuntz JL. Recurrent psoriatic onychopariostitis induced by hydroxychloroquine. *Rev Rhum Engl Ed*. 1995;62(11):795-7.
38. Trnavsky K, Zbojanova M, Vlcek F. Antimalarials in psoriatic arthritis. *J Rheumatol*. 1983;10(5):833-4.
39. Wolf R, Schiavo AL, Lombardi ML, de Angelis F, Ruocco V. The in vitro effect of hydroxychloroquine on skin morphology in psoriasis. *Int J Dermatol*. 1999;38(2):154-7.
40. Kuflik EG. Effect of antimalarial drugs on psoriasis. *Cutis*. 1980;26(2):153-5.
41. Abel EA. Diagnosis of Drug-Induced Psoriasis. *Semin Dermatol*. 1992;11(4):269-74.
42. Sorbara S, Cozzani E, Rebora A, Parodi A. Hydroxychloroquine in psoriasis: is it really harmful? *Acta Derm Venereol*. 2006;86(5):450-1.
43. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther*. 2007;20(4):160-74.
44. Herman SM, Shin MH, Holbrook A, Rosenthal D. The role of antimalarials in the exacerbation of psoriasis: a systematic review. *Am J Clin Dermatol*. 2006;7(4):249-57.
45. Lazarova AZ, Tsankov NK, Zlatkov NB. Psoriasis induced by topically applied indomethacin. *Clin Exp Dermatol*. 1989;14(3):260-1.
46. Katayama H, Kawada A. Exacerbation of psoriasis induced by indomethacin. *J Dermatol*. 1981;8(4):323-7.
47. Powles AV, Griffiths CE, Seifert MH, Fry L. Exacerbation of psoriasis by indomethacin. *Br J Dermatol*. 1987;117(6):799-800.
48. Lassus A. A comparative pilot study of azapropazone and indomethacin in the treatment of psoriatic arthritis and Reiter's disease. *Curr Med Res Opin*. 1976;4(1):65-9.
49. Green CA, Shuster S. Lack of effect of topical indomethacin on psoriasis. *Br J Clin Pharmacol*. 1987;24(3):381-4.
50. Mui MM, Hsia SL, Halprin KM. Further studies on adenylyl cyclase in psoriasis. *Br J Dermatol*. 1975;92(3):255-62.
51. Voorhees JJ. Leukotrienes and other lipoxygenase products in the pathogenesis and therapy of psoriasis and other dermatoses. *Arch Dermatol*. 1983;119(7):541-47.
52. Wong E, Camp RD, Greaves MW. The responses of normal and psoriatic skin to single and multiple topical applications of leukotriene B₄. *J Invest Dermatol*. 1985;84(5):421-23.
53. Lammers AM, van de Kerkhof PC. Response of polymorphonuclear leukocytes to topical leukotriene b₄ in healthy and psoriatic skin. *Br J Dermatol*. 1987;116(4):521-24.
54. Kragballe K, Herlin T. Benoxaprofen improves psoriasis. a double-blind study. *Arch Dermatol*. 1983;119(7):548-52.
55. Reshad H, Hargreaves GK, Vickers CF. Generalized pustular psoriasis precipitated by phenylbutazone and oxyphenbutazone. *Br J Dermatol*. 1983;109(1):111-3.
56. Ben-Chetrit E, Rubinow A. Exacerbation of psoriasis by ibuprofen. *Cutis*. 1986;38(1):45.
57. Meyerhoff JO. Exacerbation of psoriasis with meclizolam. *N Engl J Med*. 1983;309(8):496.
58. Paller AS, Wishner A, Roenigk HH Jr. Meclizolam for psoriasis. *Arch Dermatol*. 1984;120(4):438.
59. Wolf R, Dorfman B, Krakowski A. Psoriasiform eruption induced by captopril and chlorthalidone. *Cutis*. 1987;40(2):162-4.
60. Wolf R, Tamir A, Brenner S. Psoriasis related to angiotensin-converting enzyme inhibitors. *Dermatologica*. 1990;181(1):51-3.
61. Thakor P, Padmanabhan M, Johnson A, Pararajasingam T, Thakor S, Jorgensen W. Ramipril-induced generalized pustular psoriasis: case report and literature review. *Am J Therapeutics*. 2010;17(1):92-9.
62. Kawamura A, Ochiai T. Candesartan cilexetil induced pustular psoriasis. *Eur J Dermatol EJD*. 2003;13(4):406-7.
63. Steckelings UM, Artuc M, Wollschlager T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. *Acta Derm Venereol*. 2001;81(5):321-5.
64. Wolfer LU, Goerdts S, Schroder K, Zouboulis CC, Orfanos CE. [Interferon-alpha-induced psoriasis vulgaris]. *Der Hautarzt Z Dermatol Venerol Verwandte Gebiete*. 1996;47(2):124-8.
65. Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet*. 28 1986;1(8496):1466-8.
66. Funk J, Langeland T, Schrupf E, Hanssen LE. Psoriasis induced by interferon-alpha. *Br J Dermatol*. 1991;125(5):463-5.
67. O'Connell PG, Gerber LH, Digiovanna JJ, Peck GL. Arthritis in patients with psoriasis treated with gamma-interferon. *J Rheumatol*. 1992;19(1):80-2.
68. Georgetson MJ, Yarze JC, Lalos AT, Webster GF, Martin P. Exacerbation of psoriasis due to interferon-alpha treatment of chronic active hepatitis. *Am J Gastroenterol*. 1993;88(10):1756-8.
69. Taylor C, Burns DA, Wiselka MJ. Extensive psoriasis induced by interferon alfa treatment for chronic hepatitis C. *Postgrad Med J*. 2000;76(896):365-7.
70. Ladoyanni E, Nambi R. Psoriasis exacerbated by interferon-alpha in a patient with chronic myeloid leukemia. *J Drugs Dermatol JDD*. 2005;4(2):221-2.

71. Yurci A, Guven K, Torun E, et al. Pyoderma gangrenosum and exacerbation of psoriasis resulting from pegylated interferon alpha and ribavirin treatment of chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2007;19(9):811-5.
72. Makino Y, Tanaka H, Nakamura K, Fujita M, Akiyama K, Makino I. Arthritis in a patient with psoriasis after interferon-alpha therapy for chronic hepatitis C. *J Rheumatol.* 1994;21(9):1771-2.
73. Lombardini F, Taglione E, Riente L, Pasero G. Psoriatic arthritis with spinal involvement in a patient receiving alpha-interferon for chronic hepatitis C. *Scand J Rheumatol.* 1997;26(1):58-60.
74. Wolfe JT, Singh A, Lessin SR, Jaworsky C, Rook AH. De novo development of psoriatic plaques in patients receiving interferon alfa for treatment of erythrodermic cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 1995;32(5 Pt 2):887-93.
75. La Mantia L, Capsoni F. Psoriasis during interferon beta treatment for multiple sclerosis. *Neurol Sci.* 2010;31(3):337-9.
76. Fierlbeck G, Rassner G. Treatment of psoriasis and psoriatic arthritis with interferon gamma. *J Investig Dermatol.* 1990;95(6 suppl):138S-41S.
77. Fierlbeck G, Rassner G, Muller C. Psoriasis induced at the injection site of recombinant interferon gamma: results of immunohistologic investigations. *Arch Dermatol.* 1990;126(3):351-5.
78. Morhenn VB, Pregerson-Rodan K, Mullen RH, et al. Use of recombinant interferon gamma administered intramuscularly for the treatment of psoriasis. *Arch Dermatol.* 1987;123(12):1633-7.
79. Shiohara T, Kobayashi M, Abe K, Nagashima M. Psoriasis occurring predominantly on warts: possible involvement of interferon alfa. *Arch Dermatol.* 1988;124(12):1816-21.
80. Di Lernia V. Treatment of psoriasis in patients with hepatitis C virus infection. *Clin Exp Dermatol.* 2011;36(4):417.
81. Behnam SE, Hindiyeh R, Fife DJ, Jeffes EW III, Wu JJ. Etanercept as prophylactic psoriatic therapy before interferon-alpha and ribavirin treatment for active hepatitis C infection. *Clin Exp Dermatol.* 2010;35(4):397-8.
82. De Simone C, Paradisi A, Capizzi R, Carbone A, Siciliano M, Amerio PL. Etanercept therapy in two patients with psoriasis and concomitant hepatitis C. *J Am Acad Dermatol.* 2006;54(6):1102-4.
83. Magliocco MA, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. *J Am Acad Dermatol.* 2004;51(4):580-4.
84. Ketikoglou I, Karatapanis S, Elefsiniotis I, Kafiri G, Moulakakis A. Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol.* 2005;15(2):107-9.
85. Kartal ED, Colak H, Ozgunes I, Usluer G. Exacerbation of psoriasis due to peginterferon alpha-2b plus ribavirin treatment of chronic active hepatitis C. *Chemotherapy.* 2005;51(2-3):167-9.
86. Hellgren L. Induction of generalized pustular psoriasis by topical use of betamethasone-dipropionate ointment in psoriasis. *Ann Clin Res.* 1976;8(5):317-9.
87. Baker H, Ryan TJ. Generalized pustular psoriasis. a clinical and epidemiological study of 104 cases. *Br J Dermatol.* 1968;80(12):771-93.
88. Tsankov N, Botev-Zlatkov N, Lazarova AZ, Kostova M, Popova L, Tonev S. Psoriasis and drugs: Influence of tetracyclines on the course of psoriasis. *J Am Acad Dermatol.* 1988;19(4):629-32.
89. Counis R, Koumanov K, Rautin J, Infante R. [Antipolytic role of tetracycline: inhibition of adenylate cyclase in vitro]. *Eur J Biochem.* 1973;37(2):244-7.
90. Patel RN, Attur MG, Dave MN, et al. A novel mechanism of action of chemically modified Tetracyclines: Inhibition of COX-2-mediated prostaglandin E2 production. *J Immunol.* 1999;163(6):3459-67.
91. Forster S, Ilderton E, Summerly R, Yardley HJ. The level of phospholipase a2 activity is raised in the uninvolved epidermis of psoriasis. *Br J Dermatol.* 1983;108(1):103-5.
92. Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. *Semin Arthritis Rheum.* 2010;40(3):233-40.
93. Bergner T, Przybilla B. Psoriasis and tetracyclines. *J Am Acad Dermatol.* 1990;23(4 Pt 1):770-1.
94. Piquero-Casals J, Fonseca de Mello AP, Dal Coletto C, Fonseca Takahashi MD, Simonsen Nico MM. Using oral tetracycline and topical betamethasone valerate to treat acrodermatitis continua of hallopeau. *Cutis.* 2002;70(2):106-8.
95. Marstrand AM, Griffiths CE. Treatments for chronic palmoplantar pustular psoriasis. *Skin Therapy Lett.* 2001;6(12):3-5.
96. Cohen HB, Beerman H. The use of systemic tetracycline and ultraviolet in psoriasis: a preliminary report. *J Invest Dermatol.* 1965;44:365-6.
97. Mourao AF, Rustin M, Isenberg D. Exacerbation of psoriatic skin lesions in patients with psoriatic arthritis receiving anti-tumour necrosis factor-alpha therapy: description of 3 cases and Review of the literature. *Clin Exp Rheumatol.* 2010;28(3):408-10.
98. Iborra M, Beltran B, Bastida G, Aguas M, Nos P. Infliximab and adalimumab-induced psoriasis in Crohn's disease: a paradoxical side effect. *J Crohn's Colitis.* 2011;5(2):157-61.
99. Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: a review. *Semin Arthritis Rheum.* 2008;37(4):251-55.
100. Alabed IB, Qushmaq KA, Khan MA. Psoriasis Induced by Infliximab in a Saudi patient with Ankylosing Spondylitis. *Saudi Med J.* 2010;31(9):1054-6.
101. Fiorino G, Allez M, Malesci A, Danese S. Review article: anti TNF-alpha induced psoriasis in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2009;29(9):921-7.
102. Manni E, Barachini P. Psoriasis induced by infliximab in a patient suffering from Crohn's disease. *Int J Immunopathol Pharmacol.* 2009;22(3):841-4.
103. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: a literature review and potential mechanisms of action. *Arthritis Rheum.* 2008;59(7):996-1001.
104. Vereia MM, Del Pozo J, Yebra-Pimentel MT, Porta A, Fonseca E. Psoriasiform eruption induced by infliximab. *Ann Pharmacother.* 2004;38(1):54-7.
105. Pirard D, Arco D, Debrouckere V, Heenen M. Anti-tumor necrosis factor alpha-induced psoriasiform eruptions: three further cases and current overview. *Dermatology.* 2006;213(3):182-6.
106. Takahashi H, Hashimoto Y, Ishida-Yamamoto A, Ashida T, Kohgo Y, Iizuka H. Psoriasiform and pustular eruption induced by infliximab. *J Dermatol.* 2007;34(7):468-72.
107. Cohen JD, Bournierias I, Buffard V, et al. Psoriasis induced by tumor necrosis factor-alpha antagonist therapy: a case series. *J Rheumatol.* 2007;34(2):380-5.
108. Cuchacovich R, Espinoza CG, Virk Z, Espinoza LR. Biologic therapy (TNF-alpha antagonists)-induced psoriasis: a cytokine imbalance between tnf-alpha and IFN-alpha? *J Clin Rheumatol.* 2008;14(6):353-6.

109. Sfikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. *Arthritis Rheum.* 2005;52(8):2513-8.
110. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. *Am J Clin Dermatol.* 2008;9(1):1-14.
111. Carter JD, Gerard HC, Hudson AP. Psoriasiform lesions induced by tumour necrosis factor antagonists: a skin-deep medical conundrum. *Ann Rheum Dis.* 2008;67(8):1181-3.
112. Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. *Ann Rheum Dis.* 2006;65(3):405-7.
113. Bovenschen HJ, Kop EN, Van De Kerkhof PC, Seyger MM. Etanercept-induced lichenoid reaction pattern in psoriasis. *J Dermatol Treat.* 2006;17(6):381-33.
114. Sari I, Akar S, Birlık M, Sis B, Onen F, Akkoc N. Anti-tumor necrosis factor-alpha-induced psoriasis. *J Rheumatol.* 2006;33(7):1411-4.
115. Borrás-Blasco J, Gracia-Perez A, Nunez-Cornejo C, et al. Exacerbation of psoriatic skin lesions in a patient with psoriatic arthritis receiving adalimumab. *J Clin Pharm Ther.* 2008;33(3):321-5.
116. Mortel MR, Emer J. Prospective new biologic therapies for psoriasis and psoriatic arthritis. *J Drugs Dermatol JDD.* 2010;9(8):947-58.
117. Gupta AK, Sibbald RG, Knowles SR, Lynde CW, Shear NH. Terbinafine therapy may be associated with the development of psoriasis de novo or its exacerbation: four case reports and a review of drug-induced psoriasis. *J Am Acad Dermatol.* 1997;36(5 Pt 2):858-62.
118. Wach F, Stolz W, Hein R, Landthaler M. Severe erythema anulare centrifugum-like psoriatic drug eruption induced by terbinafine. *Arch Dermatol.* 1995;131(8):960-1.
119. Szepietowski JC. Terbinafine exacerbates psoriasis: case report with a literature review. *Acta Dermatovenerologica Croatica ADC.* 2003;11(1):17-21.
120. Fisher DA, Elias PM, LeBoit PL. Exacerbation of psoriasis by the hypolipidemic agent, Gemfibrozil. *Arch Dermatol.* 1988;124(6):854-5.
121. Proksch E. [Antilipemic drug-induced skin manifestations]. *Der Hautarzt Z Dermatol Venerol Verwandte Gebiete.* 1995;46(2):76-80.
122. Spencer JM, Silvers DN, Grossman ME. Pustular eruption after drug exposure: is it pustular psoriasis or a pustular drug eruption? *Br J Dermatol.* 1994;130(4):514-9.
123. Isogai Z, Sunohara A, Tsuji T. Pustular drug eruption due to bacampicilin hydrochloride in a patient with psoriasis. *J Dermatol.* 1998;25(9):612-5.
124. Yamamoto M, Ikeda M, Kodama H, Sano S. Transition of psoriasiform drug eruption to psoriasis de novo evidenced by histopathology. *J Dermatol.* 2008;35(11):732-6.
125. Cochran RE, Thomson J, Fleming K, McQueen A. The psoriasiform eruption induced by practolol. *J Cutan Pathol.* 1975;2(6):314-9.
126. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatolog Treat.* 2009;20(2):100-8.