Psoriasis Induced or Aggravated by Drugs

FRANCO RONGIOLETTI, CRISTINA FIORUCCI, and AURORA PARODI

ABSTRACT. Drug ingestion may result in exacerbation of preexisting psoriasis, induction of psoriatic lesions on clinically uninvolved skin in patients with psoriasis, or precipitation of the disease. In view of their relationship to psoriasis, therapeutic agents may be classified as follows: (1) drugs with strong evidence for a causal relationship to psoriasis including lithium, beta blockers, and synthetic antimalarial drugs; (2) drugs with considerable number of studies but insufficient data to support induction or aggravation of the disease; (3) drugs occasionally reported to be associated with aggravation or induction. While focusing on the most common causative agents for drug induced/aggravated psoriasis, we discuss the controversies about the relationship between drugs and psoriasis and report our own experience at the Section of Dermatology, University of Genoa. (J Rheumatol 2009;36 Suppl 83:59-61; doi:10.3899/jrheum.090227)

Key Indexing Terms:
PSORIASIS DRUGS ADVERSE EFFECTS

Drug ingestion may result in exacerbation of preexisting psoriasis, induction of psoriatic lesions on clinically uninvolved skin in patients with psoriasis, or precipitation of the disease[1-3]. In view of their relationship to psoriasis, therapeutic agents may be classified as follows: (1) drugs with strong evidence for a causal relationship to psoriasis including lithium, beta blockers, and synthetic antimalarial drugs; (2) drugs with considerable but insufficient data to support induction or aggravation of the disease; (3) drugs occasionally reported to be associated with aggravation or induction.

While focusing on the most common causative agents for drug-induced/aggravated psoriasis, we discuss the controversies about the relationship between drugs and psoriasis and report our own experience at the Section of Dermatology, University of Genoa.

DRUGS WITH STRONG EVIDENCE FOR A CAUSAL RELATIONSHIP TO PSORIASIS

Drugs with strong evidence include lithium, beta blockers, synthetic antimalarial drugs, and withdrawal of corticosteroids.

Lithium. Lithium is used in the treatment of psychosis and depression. The incidence of exacerbating and inducing psoriasis ranges from 3.4% to 45%, and induction appears to be less common than exacerbation and not always dose related. A long latency period is usually observed between starting the drug and the adverse event, with a mean time of 20 weeks for exacerbation and 48 weeks for induction. It has been suggested that psoriasis that has flared with lithium is more resistant to standard treatments. The pathogenesis of the adverse event is still unclear but the "inositol depletion hypothesis" seems to be the most reputed explanation[4].

Beta blockers. Both cardio-selective and non-cardioselective and systemic and topical beta blockers may be involved. We can observe both aggravation and induction of the psoriatic disease with a long latency period (even > 1 year)[4]. In a 1 year retrospective study of 558 psoriatic patients, 26 were taking beta blockers, and exacerbations were noted in 72.4%[5]. As for pathogenesis, a decrease of cyclic adenosine monophosphate (cAMP) induced by beta blockers could lead to a decrease in intracellular calcium and consequently increased cellular proliferation and lack of differentiation as seen in psoriasis[4].

Antimalarials. Exacerbation of psoriasis is more frequent than induction. Of 48 American soldiers with psoriasis given chloroquine as malaria prophylaxis, 20 (42%) had exacerbation of their disease[6]. Development from psoriasis vulgaris to erythrodermic or pustular psoriasis has been reported. The latency period goes from 4 to 12 weeks. The exacerbation is more common with chloroquine than hydroxychloroquine. Psoriasis cleared up completely after withdrawal of the drug in only 30% of patients taking antimalarials, as compared with more than 60% of those receiving lithium, and nearly 50% of those receiving beta blockers. This is considered evidence that antimalarial drugs only trigger latent psoriasis and do not induce psoriasis *de novo*[7]. Antimalarial drugs may inhibit transglutaminase in the skin; and as transglutaminase is thought to influence cellular proliferation, inhibition of this enzyme may aggravate psoriasis[8].

Corticosteroids. Too rapid withdrawal of topical and systemic corticosteroid therapy may precipitate pustular or erythrodermic exacerbations of psoriasis[2].

From the Section of Dermatology, DISEM, University of Genoa, Genoa, Italy.

F. Rongioletti, MD, Associate Professor; C. Fiorucci, MD, Dermatologist; A. Parodi, MD, Full Professor.

Address correspondence to Prof. F. Rongioletti, Clinica Dermatologica, viale Benedetto XV 7, 16132, Genova, Italy.
E-mail: franco.rongioletti@unige.it

DRUGS POSSIBLY RELATED TO PSORIASIS

This group includes angiotensin-converting enzyme (ACE) inhibitors, sartans (angiotensin II type 1 receptor blockers), nonsteroidal antiinflammatory agents (NSAID), antibiotics, interferons, and tumor necrosis factor–α (TNF–α) inhibitors.

Angiotensin-converting enzyme inhibitors. ACE inhibitors can trigger both induction and exacerbation of psoriasis with an intermediate latency period (4 to 12 weeks). Indeed, a hospital based case-control (110 patients, 515 controls) and case-crossover study (98 patients) in Israel reported a possible association between use of ACE inhibitors and increased relative psoriasis risk in the case-control analysis[9]. Augmentation of kinin levels in the skin seems to be the pathogenetic mechanism.

Sartans. Sartans have been associated with psoriasis, although less significantly than ACE inhibitors. A mechanism of cross-reaction with ACE inhibitors has been suggested and the mechanism seems to be related to an increase in angiotensin II, which stimulates keratinocyte proliferation.

Nonsteroidal antiinflammatory drugs. The triggering of psoriasis induced by nonsteroidal antiinflammatory drugs (NSAID) is more controversial. An adverse effect of NSAID on psoriasis is supported by a case-control and case-crossover study[9], but in one of the few large studies, only 6 of 462 psoriatic patients had exacerbation of psoriasis after taking oral NSAID[10]. The latency period is short (less than 2 weeks). Both topical and systemic NSAID have been implicated, including indomethacin, ibuprofen, phenylbutazone, naproxen, and acetylsalicylic acid. NSAID inhibit metabolism of arachidonic acid by the cyclooxygenase pathway, leading to an accumulation of leukotrienes, which may aggravate psoriasis.

Antibiotics. Antibiotics, especially tetracyclines (doxycycline), have been implicated in triggering psoriasis. However, a photosensitivity reaction inducing psoriatic lesions following a Koebner phenomenon in a psoriatic background cannot be ruled out. Evidence for penicillins (amoxicillin, ampicillin) are less relevant. An increase in epidermal cAMP could be the pathogenetic trigger.

Interferons. Interferons (IFN) have been linked to psoriasis. Most cases of triggered psoriasis are related to IFN–α and less frequently to IFN–β. Both induction and exacerbation have been observed, even at the site of injection (Koebner phenomenon?) between 1 and 6 weeks after initiation (but as long as 6 months). In some cases there is persistence even after stopping the drug and the severity of psoriasis seems to be related to IFN dosage. IFN could promote a cascade of proinflammatory cytokines favoring the appearance of psoriasis[11,12].

TNF inhibitors. TNF inhibitors have also been related to the induction/exacerbation of psoriasis. This is a paradox phenomenon, as these biologic agents have been developed for the treatment of moderate/severe psoriasis. Actually, TNF–α inhibitors induced psoriasis in 74 patients and exacerbated a preexisting psoriasis in 25 patients. All 3 TNF–α inhibitors have been involved, i.e., infliximab (63 patients), etanercept (37 patients), and adalimumab (26 patients). The mean time to appearance was 9.5 months. Cessation of TNF–α inhibitor in 47 patients resulted in complete remission in 21 patients, partial remission in 20 patients, and stable disease in another 3 patients[13].

Miscellaneous drugs. Miscellaneous drugs associated with exacerbation of psoriasis include imiquimod, cimetidine, gemfibrozil, potassium iodide, fluoxetine, and calcium antagonists[4].

CONTROVERSIES ABOUT PSORIASIS INDUCED / AGGRAVATED BY DRUGS

Psoriasis is a very common disease, and its exacerbation / induction attributed to a drug has been suggested to be coincidental. There are some clinical controversies about the true appearance of a psoriasis triggered by drugs. In fact, skin eruptions in some cases do not appear to be typical psoriasis and are described as psoriasiform. These psoriasiform reactions are less red, less thick, and less scaly, and the knees and elbows tend not to be involved[14]. Another problem is that uninvolved skin of patients with psoriasis responds to various stimuli and an adverse drug reaction in a psoriatic background may present with psoriasis via a Koebner response. In addition, psoriasis may be induced by other triggers. For instance, it has been suggested that the worsening or induction of psoriasis in the setting of an antibiotic therapy may be because of the infection and not the use of the antibiotics.

There are also some histological controversies about psoriasis induced/aggravated by drugs. Few histologic studies are available for establishing microscopic differences between the aggravated psoriasis and the drug-induced psoriasiform eruption. More controversies against a link between drugs and psoriasis have emerged from evidence-based dermatology. Too few controlled or evidence-based studies are available on this topic and most of the reports deal with small series or anecdotal cases. A recent large population-based case-control analysis from Switzerland does not support the current proposition that beta blocker use is associated with an increased risk of psoriasis, nor did the study find evidence for a substantially altered psoriasis risk for other

antihypertensive drugs[15]. Moreover, another Italian study showed no statistically significant association of psoriasis with several drugs frequently implicated in the appearance or acute exacerbation of dermatitis[16].

We performed a study at the Section of Dermatology of the University of Genoa on 85 patients with a new diagnosis of psoriasis (52 men, 33 women; mean age 53 years) compared with 85 matched controls attending our clinic for different cutaneous surgical procedures for evaluating a significant difference in drug intake. No significant difference between the 2 groups was found concerning the intake of antihypertensive drugs.

CONCLUSION

There is no strong evidence to refute or support the role of some drugs in the exacerbation of psoriasis. Drugs with the strongest evidence are lithium (induction and exacerbation), beta blockers (induction and exacerbation), and antimalarials (exacerbation). Different periods of latency (from a few weeks to many months) have been reported, and different pathogenetic mechanisms (both immunologic and nonimmunologic) are involved in relation to the different drugs. Many controversial issues are still not resolved and more studies (especially on epidemiological and immunohistological grounds) are needed. Special consideration should be given regarding drugs in psoriatic patients receiving polypharmacy or with recent worsening or poor response to conventional therapy.

REFERENCES

1. Tsankov N, Angelova I, Kazandjieva J. Drug-induced psoriasis. Recognition and management. Am J Clin Dermatol 2000;1:159-6.
2. Abel E, Di Cicco LM, Orenberg EK, et al. Drugs in exacerbation of psoriasis. J Am Acad Dermatol 1986;15:1007-22.
3. Dika E, Varotti C, Bardazzi F, Maibach KI. Drug-induced psoriasis: an evidence-based overview and the introduction of psoriatic drug eruption probability score. Cutan Ocul Toxicol 2006;2:1-11.
4. Fry L, Baker BS. Triggering psoriasis: the role of infections and medication. Clin Dermatol 2007;25:606-15.
5. Gold MH, Holy J, 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;19:837-41.
6. Kuflik EG. Effects of antimalarial drugs on psoriasis. Cutis 1980;26:153-5.
7. 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;7:249-57.
8. Wolf R, Lo Schiavo A, Lombardi A, Esposito C, Ruocco V. The in vitro effect of hydroxychloroquine on skin morphology and transglutaminase. Int J Dermatol 1997;36:704-7.
9. Cohen AD, Bonneh DY, Reuveni H, Vardy DA, Naggan L, Halevy S. Drug exposure and psoriasis vulgaris: case-control and case-crossover studies. Acta Derm Venereol 2005;85:299-303.
10. Tsankov N, Botev-Zlarkov N, Lazarova AZ. Psoriasis and drugs. J Am Acad Dermatol 1988;19:629-32.
11. Funk J. Psoriasis induced by alpha-interferon. Br J Dermatol 1991;1254:463-5.
12. Navne JE, Hedegaard U, Bygum A. Activation of psoriasis in patients undergoing treatment with beta-interferon [Danish]. Ugeskr Laeger 2005;167:2903-4.
13. Wollina U, Hansel G, Koch A, Schönlebe J, Köstler 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;9:1-14.
14. Heng MC, Heng MK. Beta-adrenoceptor antagonist induced psoriasiform eruption. Clinical and pathogenetic aspects. Int J Dermatol 1988;27:619-27.
15. Brauchli YB, Jick SS, Curtin F, Meier CR. Association between beta blockers, other antihypertensive drugs and psoriasis: population-based case-control study. Br J Dermatol 2008;158:1299-307.
16. Naldi L, Chatenoud L, Belloni A, et al. Medical history, drug exposure and the risk of psoriasis. Evidence from an Italian case control study. Dermatology 2008;216:125-30.