Aggravation of psoriasis by antimalarials: A comment on the pathogenic mechanism

Sir,

Exacerbation of psoriasis in patients taking antimalarials is mentioned in all dermatology textbooks, but the underlying mechanism has not been explained in full. It is estimated that up to 18% of patients with psoriasis would develop an exacerbation of their disease following antimalarial therapy. In contrast to lithium and beta blockers, antimalarials do not induce psoriasis *de novo,* but they only trigger already existing psoriasis, via a pharmacologic mechanism, probably due to an alteration of the activity of enzymes involved in the epidermal proliferation process. Wolf *et al.*[1] have shown that hydroxychloroquine inhibited transglutaminase activity in a concentration-dependent manner. This is suggested to cause an initial break in the barrier function of the epidermis, followed by a physiologic response of the epidermis aimed at barrier restoration. This rather nonspecific stimulus to epidermal proliferation is suggested to be sufficient to trigger psoriasis in predisposed individuals. That antimalarial drugs only trigger latent psoriasis and do not induce psoriasis *de novo* can be suspected from the fact that psoriasis cleared up completely after withdrawal of the drug in only 30% of patients on antimalarials, as compared with more than 60% of those receiving lithium and nearly 50% of those receiving beta blockers. This is probably also why the incubation period of the cases induced by antimalarial drugs is much shorter than that of the cases induced by lithium and beta blockers. Possibly, in triggered psoriasis (as in antimalarials), the drug only sets off with a chain of pathologic events previously programmed and ready to be set off; whereas in true drug-induced cases (as in some cases induced by lithium and beta blockers), the drug is supposed to cause more profound changes and therefore more time is needed for these changes to occur.[1,2]

Herein, I would like to suggest that antimalarials' induction of psoriasis could be partly attributed to their inhibition of cholesterol biosynthesis as well.

Cholesterol biosynthesis by keratinocytes is documented to be fundamental to the integrity of epidermal barrier function. It is shown that topical application of lovastatin to the skin of hairless mice led to the development of epidermal hyperplasia, erythema, scaling, and increased DNA synthesis. This effect, being secondary to the disruption of skin barrier as the result of decreased production of cholesterol by keratinocytes, was aborted with concomitant application of cholesterol.[3]

An important point needing attention is that though topically induced statins induce epidermal barrier dysfunction, the risk of exacerbation of psoriasis with orally administered statins is extremely low. In fact, it has been shown that pharmacologic doses of lovastatin do not worsen the course of psoriasis; and though gemfibrozil, an anti-triglyceride agent, has been reported to exacerbate psoriasis, statins have not been reported to do so; and even the lovastatin manufacturer (Merck Sharp and Dome, Rahway, NJ, USA) has anecdotal evidence that the condition of some psoriatic subjects improves when this drug is administered. It is most likely that the beneficial immunomodulatory effects of statins on immunocytes outweigh their untoward effect on surface lipids or they have not enough bioavailability to keratinocytes to affect keratinocytic cholesterol synthesis.[4]

There are several reports of aggravation of psoriasis with terbinafine, which is explained by the ability of this agent to inhibit squalene epoxidase, a pivotal enzyme in mammalian cholesterol biosynthesis.[5]

Interestingly, both chloroquine and hydroxychloroquine are reported to significantly decrease serum cholesterol levels, hence neutralizing the dyslipidemia seen in systemic lupus erythematosus patients taking steroids.[6,7] Chloroquine is shown to be a potent inhibitor of cholesterol biosynthesis by isolated rat hepatocytes. It does not affect fatty acid synthesis by isolated hepatocytes, suggesting that it acts on the cholesterol biosynthetic pathway beyond the cytosolic acetyl-coA branch-point of cholesterol and fatty acid synthesis.[8]

Therefore, it could be deduced that antimalarials' inhibition of cholesterol biosynthesis contributes to the epidermal barrier dysfunction induced by their transglutaminase inhibition, which can exacerbate psoriasis in genetically predisposed individuals by triggering epidermal hyperproliferation. This dual mechanism explains the relatively high incidence of aggravation of psoriasis by these agents, which has attracted the attention of all authors of dermatology textbooks.

M. R. Namazi
Department of Dermatology, Shiraz University of Medical Sciences, Shiraz, Iran

Address for correspondence: M.R. Namazi, Dermatology Department, Faghihi Hospital, Shiraz, Iran. E-mail: namazi_mr@yahoo.com

REFERENCES

1. Wolf R, Ruocco V. Triggered psoriasis. Adv Exp Med Biol 1999;455:221-5.
2. 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;38:154-7.
3. FeingoldK R, Mac-QiangM, PredschE, MenonG K, BrownB E, EliasP M. The lovastatin-treated rodent: A new model of barrier disruption and epidermal hyperplasia. J Invest Dermatol 1991;96:201-9.
4. Namazi MR. Statins: Novel additions to the dermatologic arsenal? Exp Dermatol 2004;13:337-9.
5. Szepietowski JC. Terbinafine exacerbates psoriasis: Case report with a literature review. Acta Dermatovenerol Croat 2003;11:17-21.
6. Ardoin SP, Sandborg C, Schanberg LE. Management of dyslipidemia in children and adolescents with systemic lupus erythematosus. Lupus 2007;16:618-26.
7. Woźniacka A, Lesiak A, Smigielski J, Sysa-Jedrzejowska A. Chloroquine influence on lipid metabolism and selected laboratory parameters. Przegl Lek 2005;62:855-9.
8. Beynen AC, van der Molen AJ, Geelen MJ. Inhibition of hepatic cholesterol biosynthesis by chloroquine. Lipids 1981;16:472-4.