

ACITRETIN TREATMENT IN PSORIASIS MAY INFLUENCE THE CELL MEMBRANE FLUIDITY

CAROLINA NEGREI¹, ANDREEA LETIȚIA ARSENE², CORINA DALIA TODERESCU³, DANIEL BODA^{4*}, MIHAELA ILIE¹

¹*Department of Toxicology, "Carol Davila" University of Medicine and Pharmacy, 6, Traian Vuia street, Bucharest, Romania*

²*Department of Biochemistry, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Traian Vuia 6, Bucharest, Romania*

³*"Vasile Goldis" Western University of Arad, 91-93, L. Rebreanu Str., Arad, Romania*

⁴*Center of Excellence in Dermato-oncology, "Carol Davila" University of Medicine and Pharmacy, 22-24 Gr. Manolescu street, Bucharest, Romania*

**corresponding author: daniel.boda@yahoo.com*

Abstract

Psoriasis is a chronic recurring condition that varies in severity from minor localized patches to complete body coverage. In this disease the normal cycle of replacing old skin cells with new one becomes unbalanced. The most popular parameter to characterise plasma membrane is fluidity. The membrane fluidity in psoriatic patients decreases. The present paper is intended to review the literature data on the possible involvement of membrane fluidity in psoriatic patients; a special focus is given to patients treated with acitretin.

Rezumat

Psoriazisul este o afecțiune cronică, recurentă, care variază ca severitate, de la leziuni minore până la leziuni care acoperă întreg corpul. În cadrul acestei boli, ciclul normal de înlocuire a celulelor îmbătrânite cu altele noi este perturbat. Cel mai popular parametru utilizat în caracterizarea membranei plasmatică este fluiditatea. Fluiditatea membranelor în cazul pacienților cu psoriazis scade, conform datelor din literatura de specialitate. Lucrarea de față analizează și sumarizează datele din literatură privind o posibilă implicare a fluidității membranare la pacienții cu psoriazis, o atenție specială acordându-se celor tratați cu acitretin.

Keywords: psoriasis, membrane fluidity, acitretin

Introduction

Current state of knowledge in psoriasis

Psoriasis is a common, chronic, recurrent inflammatory disease of the skin characterized by circumscribed erythematous, dry, scaling plaques of various sizes, covered by silvery white lamellar layers [1]. Skin cells

become mature and shed in about a month. However in psoriasis, the normal cycle of replacing old skin cells with new one becomes unbalanced (skin cells reproduce faster than normal and live only three to four days) [2]. The exact pathogenesis is unknown, but an important and active role in the pathogenesis of psoriasis has been attributed to changes in cutaneous blood vessels. All investigations showed elongated, widened, and tortuous microvessels in the papillary dermis; investigations were made with confocal laser scanning microscope (Figures 1 and 2) [3,4].

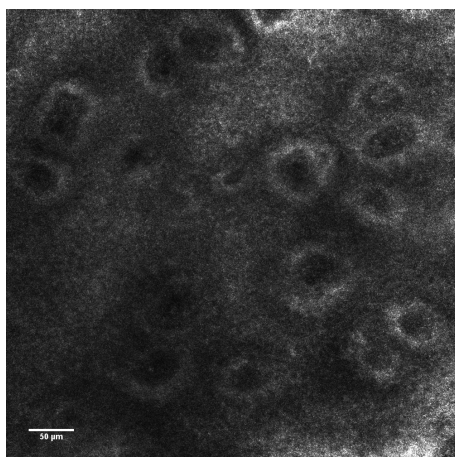


Figure 1. Normal skin

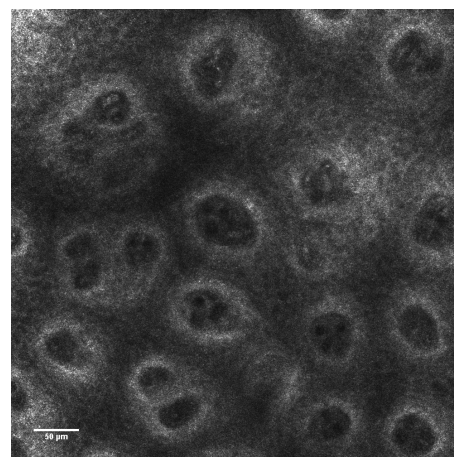


Figure 2. Skin in psoriasis

Among the most cited factors that favor psoriasis development are the genetic conditioning, trauma, skin infection, drugs, emotional stress, alcohol and smoking [5,6,7]. The accelerated proliferation and abnormal differentiation of epidermal keratinocytes is a reaction to the activation of the immune system in focal skin regions, which in turn is mediated by activated CD^{8+} and CD^{4+} T lymphocytes that accumulate in the affected skin [8].

Psoriasis is difficult to treat, due to incomplete understanding of the factors behind its pathogenesis.

Current state of the psoriasis treatment with acitretin

The oral retinoids are vitamin-A derivatives that have been used to treat psoriasis since the early 1980s. Although their exact mechanism of action in the treatment of psoriasis is not completely understood, retinoids are known to modulate epidermal proliferation and differentiation and to have immunomodulatory and anti-inflammatory activity.

Etretinate was the first aromatic retinoid introduced in the dermatological practice. It is well established that etretinate, like all

retinoids, exerts its effect on the gene expression via the cellular all-*trans*-retinoic acid receptor [9] and 9-*cis*-retinoid receptor [10,11], which belong to the steroid receptor family. This drug appeared to be highly effective in psoriasis (palm and sole psoriasis); however, its exact mechanism of action in psoriasis is unknown. Although etretinate is not used in clinical practice anymore, being replaced by its metabolite, acitretin, its therapeutic efficacy is undeniable.

Acitretin response is relatively slow, with a 3- to 6- month period required to achieve a maximal response. Appropriate dosing must take into account the balance between safety, tolerability, and efficacy as many patients may not tolerate the higher doses of acitretin to achieve optimal efficacy. For these reasons, the combination of retinoids and UV light therapy may be considered feasible and appropriate.

Because acitretin is not immunosuppressive, it has also been used in combination with biologic therapies and in the treatment of choice in HIV-positive patients with severe psoriasis [12].

Acitretin's major side effect is its teratogenicity, and its use is, therefore, limited to male and female patients of nonchildbearing potential. At high doses, it may be associated with significant mucocutaneous effects along with hair loss. Because of the known organ toxicities of traditional systemic agents, the concept of rotational therapy was developed so that patients could rotate from one agent to the other or to phototherapy or photochemotherapy to minimize total cumulative dose and thereby limit toxicity [13]. With the advent of biologic therapies, and their reduction in incidence of major organ toxicity, rotational therapy is less commonly used [14].

Acitretin is FDA (Food and Drug Administration) pregnancy category X (highly unsafe during pregnancy, with the risk of use outweighing any possible benefit). The use of any dose of acitretin during pregnancy may lead to numerous malformations, including cardiovascular, ocular, auditory, central nervous system, craniofacial and skeletal, with the greatest risk occurring between the third and sixth weeks of gestation [15]. Although the half-life of acitretin is 49 hours, acitretin may transform either spontaneously, or as a result of alcohol ingestion, into etretinate, which has a half-life of 168 days. Based on this long half-life, it can take up to 3 years for etretinate to be eliminated from the body.

Studies of the acitretin treatment effect on cell membrane fluidity

It has been shown that all-*trans* retinoic acid and its derivative etretinate can influence the cell membrane, modifying the metabolism of red

cell membrane proteins [16], membrane transport [17] and its fluidity [18-20].

The functioning of biological membranes is, to a large extent, determined by the structure and dynamics of their liquid-crystalline lipid bilayers. The most popular parameter to characterise plasma membrane is its fluidity. Membrane fluidity, which can be associated with the inverse of the local microviscosity, reflects the ordering and dynamics of phospholipid acyl chains in the membrane bilayers. A number of studies have demonstrated that plasma membrane is a heterogeneous structure with several coexisting domains with different fluidity characteristics [21-24].

Membrane fluidity was studied by electron paramagnetic resonance (EPR) spin-labeling technique. The line shape of experimental spectra was compared with calculated spectra by the model based on the lateral heterogeneity of cell membrane with several coexisting domains of different fluidity and dynamics [25].

The most popular technique to evaluate cell membrane fluidity changes was during the last two decades the use of appropriate fluorescent probes, such as fluorescent-labeled fatty acids analogues and phospholipids, 1,6-diphenylhexatriene (DPH) and its derivatives, anilinonaphtalene sulfonate (ANS) derivatives, DCVJ, laurdan, prodan [26]. Techniques vary from steady-state or time resolved fluorescence spectroscopy (with or without fluorescence polarization), to flow cytometry and fluorescence microscopy.

A large number of observations indicate that psoriasis is linked to plasma membrane alterations in different types of cells [27,28]. Some authors suggest that psoriasis might be a widespread membrane disorder [16,17,29]. Therefore, it is possible that etretinate exerts its therapeutic effect in psoriasis also through an action on the cell membrane. Simonetti and Messini (1989) have shown that etretinate applied to psoriatic patients even in low doses (0.3 mg/kg body weight) caused a significant increase in erythrocyte membrane fluidity as compared with values before treatment.

Basal fluidity of erythrocyte membranes in psoriatic patients is different from healthy ones, but this difference does not seem to be linked to membrane [30] lipid composition or plasma lipid profile. These results are in agreement with those reported by other authors [28]. The membrane fluidity of erythrocytes was decreased more evidently in the deeper hydrocarbon domains of the bilayer than in the polar head region, because of the different effect of lipid peroxidation on membrane fluidity. The membrane fluidity in psoriatic patients treated orally with etretinate (0.8–1.0 mg/kg body weight) increases, as treatment progressed [20,30]. Although

membrane fluidity is generally influenced by the membrane phospholipid composition [31-33], there was no alteration in the membrane lipid composition of erythrocytes from patients treated with etretinate [20,30] found slight (but not statistically significant) changes in phospholipid fatty acid composition and cholesterol-to-protein ratio during etretinate therapy. This discrepancy may result from the fact that etretinate may inhibit the enzymatic deacylation of arachidonic acid from membrane phospholipids *via* phospholipase A2 [34]. Since etretinate is no longer used in clinical practice, similar *in vivo* and some *in vitro* experiments using its metabolite acitretin were performed, because clinical experiments have revealed that acitretin can be transformed into etretinate under some conditions.

In 2006, some studies [35] showed that acitretin, even at low concentrations, is capable of inducing the reduction of red cell deformability. A reduced tendency of acitretin-treated RBCs (red blood cells) to deform might result from the ability of acitretin to perturb the cell shape and membrane viscoelastic properties.

References

1. James WD, Berger TG, Elston DM, editors. *Andrew's Diseases of the skin Clinical Dermatology*, 10th edition. Canada:Saunders Elsevier; 2006, 193-201
2. Luty-Frackiewicz A, Gorka IM, Januszevska L. Influence of smoking and alcohol consumption on total antioxidant status in patients with psoriasis. *Adv Clin Exp Med*. 2006, 15(3), 463-9.
3. Archid R, Patzelt A, Lange-Asschenfeldt B, Ahmad S, Ulrich M, Stockfleth E, Philipp S, Sterry W, Lademann J, Confocal laser scanning microscopy of capillaries in normal and psoriatic skin, *Journal of Biomedical Optics*, *in press*
4. Caruntu C, Boda D, Evaluation through *in vivo* reflectance confocal microscopy of the cutaneous neurogenic inflammatory reaction induced by capsaicin in human subjects, *Journal of Biomedical Optics*, *in press*
5. McGrath JA, Eady RA, Pope FM. Anatomy and organization of human skin. Rook's T.B. *Of Dermatology Volume One* 7th ed. 2004, 3.1-3.84.
6. Wolters M, Diet and psoriasis: experimental data and clinical evidence. *Br. J Dermatol* 2005, 153, 706-14
7. Cojocaru M, Cojocaru IM, Radu-Popescu MA, Arsene AL, The relationship between vaccination and the development of autoimmune diseases *Farmacia* 2010, 58(6), 677-85
8. Tlacuilo-Parra JA, Guevara-Gutierrez E, Rodriguez-Castellanos MA et al. Leflunomide in the treatment of psoriasis: results of a phase II open trial'. *Br J Dermatol* 2004, 150, 970-6.
9. Geiger JM. Efficacy of acitretin in severe psoriasis. *Skin Therapy Lett* 2003, 8, 1-3, 7.
10. Vincent V, Zabraniecki L, Loustau O, Godfrin B, Latour FB, Railhac JJ, et al. Acitretin-induced enthesitis in a patient with psoriatic arthritis. *Joint Bone Spine* 2005, 72, 326-9.
11. Yamauchi PS, Rizk D, Kormilli T, Patnaik R, Lowe NJ. Systemic retinoids. In: Weinstein GD, Gottlieb AB, editors. *Therapy of moderate to severe psoriasis*. New York: Marcel Dekker Inc, 2003, 137-50.
12. Buccheri L, Katchen BR, Karter AJ, Cohen SR. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol* 1997, 133, 711-5.
13. Ling MR. Acitretin: optimal dosing strategies. *J Am Acad Dermatol* 1999, 41(Suppl), 13-7.

14. Menter MA, See JA, Amend WJ, Ellis CN, Krueger GG, Lebwohl M, *et al.* Proceedings of the Psoriasis Combination and Rotation Therapy Conference; Deer Valley, UT; October 7-9, 1994. *J Am Acad Dermatol* 1996, 34, 315-21.
15. Kumar R, Weiss VC, West DP, Chiero LA, Erythrocyte membrane phosphorylation in untreated and in etretinate-treated psoriatic. *Br. J. Dermatol.* 1983, 109, 277-286.
16. Gornicki A, Domain structure of erythrocyte membranes in psoriasis: an EPR study *J Dermatol Sci.* 2002, 29(3), 214-221
17. Varani J, Burmeister W, Bleavins MR, Johnson K, All-*trans* retinoic acid reduces membrane fluidity of human dermal fibroblasts. *Am. J. Pathol.* 1996, 148, 1307-1312.
18. Wassall SR, Stillwell W, Interactions of retinoids with phospholipid membranes: electron spin resonance. *Methods Enzymol* 1990, 189, 383-394.
19. Simonetti O, Messini L, Effect of etretinate on fluidity and lipid composition of the erythrocyte membrane in patients with psoriasis. *G. Ital. Dermatol. Venereol.* 1989, 124, 493-497.
20. Edidin M. Lipid microdomains in cell surface membranes. *Curr Opin Struct Biol* 1997, 7, 528-32.
21. Jorgensen K, Ipsen JH, Mouritsen OG. Lipid-bilayer heterogeneity. *Princip Med Biol A* 1997, 7, 19-38.
22. Welti R, Glaser M. Lipid domains in model and biological membranes. *Chem Phys Lipids* 1994, 73, 121-37.
23. Karnovsky MJ, Kleinfeld AM, Hoover RL, Klausner RD. The concept of lipid domains in membranes. *J Cell Biol* 1982, 94, 1-6.
24. Cooper RA, Abnormalities of cell membrane fluidity in the pathogenesis of disease. *N. Engl. J. Med.* 1977, 297, 371-377.
25. Strancar J, Sentjerc M, Sachara M. Fast and accurate characterization of biological membranes by EPR spectral simulations of nitroxides. *J Magn Reson* 2000, 142:254-65.
26. *** The Molecular Probes® Handbook - A Guide to Fluorescent Probes and Labeling Technologies, <http://www.invitrogen.com/site/us/en/home/References/Molecular-Probes-The-Handbook.html>
27. DiCicco LM, Fraki JE, Mansbridge JN, The plasma membrane in psoriasis. *Int. J. Dermatol.* 1987, 26, 631-638.
28. Gornicki A, Gutszer A, *In vivo* and *in vitro* influence of etretinate on erythrocyte membrane fluidity *Eur J Pharmacol.* 2001, 423(2-3), 127-34
29. Mahrle G, Orfanos CE, The plasma unit membrane. Membrane mediated growth control and its failure in psoriasis. *Br. J. Dermatol.* 1977, 96, 215-223.
30. Gornicki A., Gutszer A. Erythrocyte membrane fluidity changes in psoriasis: an EPR study *J Dermatol Sci.* 2001, 27(1), 27-30
31. Nițulescu-Arsene AL, Mitrea N, Cristea A, Dragoi CM, Experimental research on mice regarding the implication of melatonin in pain management *Farmacia*, 2009, 2, 223-28
32. Nițulescu-Arsene AL, Arama C, Mitrea N, Cristea A, Experimental assesement of cerebral monoaminergic status in a murine model of behavior *Farmacia*, 2009, 4, 492-9
33. Nigam S, Inhibition of lipxygenase products by retinoids in human blood cells. *Dermatologica* 1987, 15Suppl. 1., 73-80.
34. Gornicki, A., Electron paramagnetic resonance EPR studies on membrane fluidity in erythrocytes from psoriatic patients, 1999, Thesis. The Ludwig Rydygier University of Medical Sciences. Bydgoszcz.

Manuscript received: December 7th 2011