Tranilast could has potential therapeutic value in the treatment of psoriasis

Kamran Mansouri *, Hamid Reza Mohammadi Motlagh, Maryam Keshavarz

Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

Introduction

Psoriasis is a phlogistic skin condition characterized by different properties such as capillaries dilation as an early histological change, proliferation of endothelial cells, neovascularization, and hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocyte infiltration, mostely consisting T lymphocyte in the late psoriasis lesions [1–4]. The involvement of inflammatory factors and angiogenic growth factors has been described in injured psoriatic skin. The inflammatory markers such as IFNγ, IL-1, IL-2, TNFα, TGFα and β, IL-6, IL-8, amphiregulin and monocyte chemoattractant protein 1(MCP-1) have been reported present in higher concentrations in psoriasis patients than in healthy peoples [5–8].

Among the angiogenic factors, recent studies have extended earlier data linking several angiogenic molecules to psoriasis, including matrix metalloproteases (MMPs) [9], vascular endothelial growth factor (VEGF), Placenta growth factor, angiopoietin and hypoxia inducible factor [10–18]. Clinical studies have also demonstrated that the activated keratinocyte in injured epidermis are the major source of pro-angiogenic mediators in psoriasis. On the other hand, the increased expression of VEGF in psoriasis lesions and an association between serum VEGF levels and disease severity have been revealed. Thus, the inhibition of endothelial cell adhesion and migration may constitute a novel therapeutic strategy for the treatment of psoriatic skin associated with excessive neovascularization [5,19]. VEGF is probabaly the most important pro-angiogenic cytokine. Furthermore, VEGF and Ang-2 act synergistically in vitro to induce endothelial cell cycle progression, migration and tube formation [15,20].

Further evidence for the role of VEGF-mediated angiogenesis in psoriasis comes from the study of a transgenic mouse model in which over expression of VEGF in the epidermis develop a phenotype closely resembling human psoriasis [21].

At least two VEGF inhibitors are tested in advanced clinical development for psoriasis: retinoids as well as modulating keratinocyte differentiation and proliferation possess anti-angiogenic activity via modulation of VEGF production [22] and Cyclosporin A which may mediate its effect through the modulation of VEGF [23], and are more poised to enter to clinical practice.

Various anti-angiogenesis therapies could provide clinical benefit in psoriasis. However, oral administration of Neovastat AE-941, a soluble extract of shark cartilage with anti-VEGF and anti-matrix metalloproteinase activities, in 49 patients with psoriasis was found to improve psoriasis area and severity index [24].

Furthermore, keratinocytes produce many factors such as IL-6, IL-8, transforming growth factor α and β (TGF-α and β), and amphiregulin. TGF-α and amphiregulin induce overproliferation of keratinocytes and with TGF-β; they are also ligands for IL-1 and epidermal growth factor receptor (EGF-R) whose expression is increased in psoriasis. Furthermore, IL-8 stimulates keratinocytes proliferation and is also a chemoattractant for neutrophils [7,8].

The properties of vascular system also undergo changes such as capillaries dilation and tortuosity, angiogenesis, and high

* Corresponding author. Address: Medical Biology Research Center, P.O. Box 1568, Sorkheh Ligeh, Kermanshah, Iran. Tel.: +98 831 4276473; fax: +98 831 4276471.

E-mail address: kmansouri@kums.ac.ir (K. Mansouri).

endothelial venules (HEV) formulation in the dermis of psoriatic lesions. The capillary dilation may be helpful for the hyperproliferating skin nourishment. Angiogenesis and hyperpermeability are also occur during increased production of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by keratinocytes which have been previously induced by TGF-α produced by both keratinocytes and lymphocytes [25–27].

Endothelial ICAM-1 is also an important factor due to interaction with LFA-1 on T lymphocytes, which is a key step in the trafficking of T lymphocytes to the affected skin, [28]. Furthermore, IFN-γ, TNF-α, and IL-1 up-regulate ICAM-1 expression in vascular endothelial cells, promoting angiogenesis. A study has also demonstrated that the expression of TNF-α, in comparison to its expression in normal skin, is increased more in both keratinocytes and vascular endothelial cells in psoriatic skin [29,30]. Another study has shown that HEV formation may be important for the extravasaion and trafficking of T-lymphocytes, inflammatory cytokines from T-lymphocytes – the chemical mediators of this change are beginning to be studied but are not defined yet [31,32].

Recently, the overexpresseion of MCP-1 has been reported in the basal keratinocytes and thus important in regulation of the interaction between proliferating keratinocytes and dermal macrophages in psoriasis pathogenesis [33,34].

Tranilast and psoriasis

Psoriasis share similar pathogenic features of increased angiogenesis steps: proliferation, migration and capillary formation. Furthermore, hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocytes and overexpression of various proinflammatory cytokines have been demonstrated in psoriatic patients. Consequently, any mechanism that could strongly suppress angiogenesis steps by inhibition of the angiogenic factors, proinflammatory cytokines and hyperproliferation of keratinocytes may control psoriasis [6,35,36]. Therefore, we propose the hypothesis that local administration of tranilast may be effective in psoriasis treatment process.

Tranilast (INN, brand name Rizaben and Tranpro) is an antiallergic drug. It was developed by Kissei Pharmaceuticals and was approved in 1982 for use in Japan and South Korea for bronchial asthma. Indications for keloid and hypertrophic scar were added in 1993. It has been used for the treatment of allergic disorders such as asthma, allergic rhinitis and atopic dermatitis, which is marketed in Asia. This drug is approved by the committee on Drugs of Japans central Pharmaceutical Affairs Council. It has also been investigated for use as an antiproliferative drug on drug-eluting stents. (1) A phase II trial is recruiting rheumatoid arthritis patients. (2) A phase III trial is evaluating tranilast for Pterygium [37,38].

Several studies on tranilast showed that it is also effective in cancer treatment in some pathways like inducing the apoptosis [39]. The administration of tranilast inhibits tumor angiogenesis in vivo and in vitro and its mechanisms may include the suppression of pro-angiogenic factors, namely VEGF, PDGF, MMP2, 9 and down-regulation of the expression of several VEGF pathway related genes [40,41]. Another study reported that the increase in TGF-β promote angiogenesis through increasing the synthesis of extracellular matrix components. Thus, this agent prevents angiogenesis through interference with TGF-β effects and also reducing collagen synthesis in keloid cells [42,43]. On the other hand, proinflammatory transcription nuclear factor-κB (NF-κB) is blocked by tranilast [44]. NF-κB is necessary for up-regulation of many proinflammatory genes such as endothelial cell adhesion molecules (ICAM-1, VCAM-1, and E-selectin), cytokines [i.e., tumor necrosis factor (TNF-α and -β, interleukin (IL-2, -6, and -8), interferon β, immunologic mediators, and also other transcription factors such as MCP-1 gene expression [45,46].

These data collectively indicate that local use of tranilast may be a good choice for psoriasis treatment due to its strong inhibitory effect on cytokines and angiogenic factors which play roles in psoriasis. Before clinical application, tranilast should be tested in animal models of psoriasis.

Conflicts of interest statement

None Declared.

References

[1] Moretti S, Spallanzani A, Pinzi C. Skin angiogenesis: biologic bases for pathological processes. Clin Dermatol 1999;17:629–31.
[2] Malhotra R, Stenn KS, Fernandez LA, et al. Angiogenic properties of normal and psoriatic skin associate with epidermis, not dermis. J Invest Dermatol 1989;61:162–5.
[3] Folkman J. Angiogenesis in psoriasis: therapeutic implications. J Invest Dermatol 1972;59:40–3.
[4] Menter A, Griffiths C. Psoriasis 2: current and future management of psoriasis. Lancet 2007;370:272–84.
[5] Leong TT, Fearon U, Veale DJ. Angiogenesis in psoriasis and psoriatic arthritis: clues to disease pathogenesis. Curr Rheumatol Rep 2005;7:325–9.
[6] Michael L, Shelling BS, Daniel G, et al. Psoriasis and vascular disease: an unsolved mystery. Am J Med 2008;121:360–5.
[7] Chong Benjamin F, Wong Henry K. Immunobiologics in the treatment of psoriasis. Clin Immunol 2007;123(2):129–38.
[8] Pietrzak AT, Zalewska A, Chodorowska G, et al. Cytokines and anticytokines in psoriasis. Clin Chim Acta 2008;394(1–2):7–21.
[9] Suomela S, Kariniemi AL, Impola U, et al. Matrix metalloproteinase-9 is expressed by keratinocytes in psoriasis. Acta Derm-Venereol 2003;83:108–14.
[10] Detmar M, Brown LF, Claffey KP, et al. Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. J Exp Med 1994;180:1141–6.
[11] Bhushan M, McLaughlin B, Weiss JB, Griffiths CEM. Levels of endothelial cell stimulating angiogenesis factor and vascular endothelial growth factor are elevated in psoriasis. Br J Dermatol 1999;141:1054–60.
[12] Simonetti O, Lucarini G, Goteri G, et al. VEGF is likely a key factor in the link between inflammation and angiogenesis in psoriasis: results of an immunohistochemical study. Int J Immunopathol Pharmacol 2006;19:751–60.
[13] Failla CM, Zambruno G, Teresa Odorisio T, Cianfarani F. The placenta growth factor in skin angiogenesis. J Dermatol Sci 2006;41:11–9.
[14] Kuroda K, Sapadin A, Shoji T, Fleischmajer R, Lebwohl M. Altered expression of angiopoietins and tie-2 endothelium receptor in psoriasis. J Invest Dermatol 2001;116:713–20.
[15] Holash J. Vessel cooption, regression and growth in tumors. Mediated by angiopoietins and VEGF. Science 1999;284:19984–8.
[16] Markham T. The relationship between clinical and angiogenic (Ang-1, Ang-2) responses to anti-TNFa therapy in severe psoriasis. Arthritis Rheum 2003;48:168.
[17] Heidenreich R, Röcken M, Ghoreschi K. Angiogenesis: the new potential target for the Therapy of Psoriasis? Drug News Perspect 2008;21:97–105.
[18] Bayliffe AI, Brigandi RA, Wilkins HJ, Levick MP. Emerging therapeutic targets in psoriasis. Curr Opin Pharmacol 2004;4:306–10.
[19] Creamer D, Sullivan D, Bicknell R, Barker J. Angiogenesis in psoriasis Angiogenesis 2002;5:231–6.
[20] Sticherling M. Mechanisms of psoriasis. Drugs Today 2005;2:275–81.
[21] Xia YP, Li B, Hylton D, Detmar M, Yancopoulos GD, Rudge JS. Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. Blood 2003;102:161–8.
[22] Vega Diaz B, Lenoir MC, Ladoux A, Frelin C, Démarchez M, Michel S. Regulation of vascular endothelial growth factor expression in human keratinocytes by Retinoids. J Biol Chem 2000;275(1):642–50.
[23] Hernández GL, Volpert OV, Íñiguez MA, et al. Selective inhibition of vascular endothelial growth factor–mediated angiogenesis by cyclosporin a: roles of the nuclear factor of activated t cells and cyclooxygenase 2. J Exp Med 2001;93(5):607–20.
[24] Sauder DN, DeKoven J, Champagne P, Croteau D, DuPont E. Neovastat (AE941) an inhibitor of angiogenesis: randomized phase I/II clinical trial results in patients with plaque psoriasis. J Am Acad Dermato 2002;l47:535–41.
[25] Krueger G, Ellis CN. Psoriasis-recent advances in understanding its pathogenesis and treatment. J Am Acad dermatol 2005;53(1):S94–S100.
[26] Michael L, Shelling A, Daniel G, Federman C, Prodanovich Srdjan, Robert S. Kirsner psoriasis and vascular disease: an unsolved mystery. Am J Med 2008;121:360–5.
[27] Bachelez H. Immunopathogenesis of psoriasis: recent insights on the role of adaptive and innate immunity. J Autoimmun 2005;25(1):69–73.
[28] Cabrijan L, Batinac T, Lenkovic M, Gruber F. The distinction between lesional and non-lesional skin in psoriasis vulgaris through expression of adhesion molecules ICAM-1 and VCAM-1. Med Hypotheses 2009;72(3):327–9.

[29] Cather JC, Cather JC, Abramovits W. Investigational therapies for psoriasis. J Am Acad Dermatol 2003;49(2):133–8.
[30] Saraceno R, Schipani C, Mazzotta A, et al. Effect of anti-tumor necrosis factor-α therapies on body mass index in patients with psoriasis. Pharmacol Res 2008;54(4):290–5.
[31] Hueber AJ, McInnes IB. Immune regulation in psoriasis and psoriatic arthritis-Recent developments. Immunol Lett 2007;114(2):59–65.
[32] Li YY, Zollner TM, Schön MP. Targeting leukocyte recruitment in the treatment of psoriasis. Clin Dermatol 2008;26(5):527–38.
[33] Deleuran MBuhl L, Ellingsen T, et al. Localization of monocyte chemotactic and activating factor (MCAF/MCP-1) in psoriasis. J Dermatol Sci 1996;13(3):228–36.
[34] Christophers E, Mrowietz U. The inflammatory infiltrate in psoriasis. Clin Dermatol 1995;13(2):131–5.
[35] Sticherling M. Mechanisms of psoriasis. Drug Discovery Today: Disease Mechanisms 2005;2(2):275–81.
[36] Levine D, Gottlieb A. Evaluation and management of psoriasis: an internist's guide. Med Clin North Am 2009;93(6):1291–303.
[37] Azuma H, Banno K, Yoshimura T. Pharmacological properties of N-(3′, 4′-dimethoxycinnamoyl) anthranilic acid (N-5′), a new anti-atopic agent. Br J Pharmacol 1976;58:483–8.
[38] http://www.fiercebiotech.com/story/press-release-nuon-therapeutics-completes-agreement-tranilast-kissei-pharmaceutical/2007-07-23.
[39] Gika M, Inoue Y, Takanami I. P-346 Anti-angiogenetic effect of N-[3, 4-dimethoxycinnamoyl]-anthranilic acid (tranilast) on non-small cell lung cancer. Abstract of the 10th World Conference on Lung Cancer 2003; 41 (2): 179.
[40] Hattori T, Wang PL. Inhibition by tranilast of nifedipine-induced proliferation of cultured human gingival fibroblasts. Eur J Pharmacol 2004;498(1–3):79–81.
[41] Isaji M, Miyata H, Ajisawa Y, Takehana Y, Yoshimura N. Tranilast inhibits the proliferation, chemotaxis and tube formation of human microvascular endothelial cells *in vitro* and angiogenesis *in vivo*. Br J Pharmacol 1997;122(6):1061–6.
[42] Pinkas J, Teicher BA. TGF-β in cancer and as a therapeutic target. Biochem Pharmacol 2006;72(5):523–9.
[43] Yamada H, Tajima S, Nishikawa T. Tranilast inhibits collagen synthesis in normal, scleroderma and keloid fibroblasts at a late passage culture but not at an early passage culture. J Dermatol Sci 1995;9(1):45–7.
[44] Spiecker M, Lorenz I, Marx N, Darius H. Tranilast inhibits cytokine-induced nuclear factor kappaB activation in vascular endothelial cells. Mol Pharmacol 2002;62(4):856–63.
[45] Karin M, Delhase M. The IκB kinase (IKK) and NF-κB: key elements of proinflammatory signaling. Semin Immunol 2000;12(1):85–98.
[46] Namazi MR, Soma J. Tranilast: a novel weapon against insulin resistance. Med Hypotheses 2005;64(6):1135–7.