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# Tranilast could has potential therapeutic value in the treatment of psoriasis

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## 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, mostly 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 IFN $\gamma$ , IL-1, IL-2, TNF $\alpha$ , TGF $\alpha$  and  $\beta$ , 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 probably 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  $\alpha$  and  $\beta$  (TGF- $\alpha$  and  $\beta$ ), and amphiregulin. TGF- $\alpha$  and amphiregulin induce overproliferation of keratinocytes and with TGF- $\beta$ ; 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

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endothelial venules (HEV) formation 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- $\alpha$  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- $\gamma$ , TNF- $\alpha$ , and IL-1 up-regulate ICAM-1 expression in vascular endothelial cells, promoting angiogenesis. A study has also demonstrated that the expression of TNF- $\alpha$ , 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 extravasation 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 overexpression 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 anti-allergic 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 Japan's 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- $\beta$  promote angiogenesis through increasing the synthesis of extracellular matrix components. Thus, this agent prevents angiogenesis through interference with TGF- $\beta$  effects and also reducing collagen synthesis in keloid cells [42,43]. On the other hand, proinflammatory transcription nuclear factor- $\kappa$ B (NF- $\kappa$ B) is blocked by tranilast [44]. NF- $\kappa$ B 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- $\alpha$  and - $\beta$ , interleukin (IL-2, -6, and -8), interferon  $\beta$ ,

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.

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