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Review Article

The role of vascular endothelial growth factor as a potential therapy of psoriasis vulgaris: A literature review

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Abstract Psoriasis management remains a challenge due to the difficulty of achieving therapeutic targets which are influenced by factors such as varying degrees of psoriasis, lack of therapeutic efficacy, and side effects of therapy. Various efforts are being made to find the best and most effective therapy. Pathogenesis of psoriasis is influenced by T cells, skin vascular disorders also play an important role. Angiogenesis in psoriasis is mediated by vascular endothelial growth factor (VEGF), angiopoietin, tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and interleukin-17 (IL-17). VEGFA inhibitors still have not received approval in psoriasis therapy, however two case reports of psoriasis patients with 40% and 50% lesion areas experienced significant improvement after bevacizumab administration. The angiogenic factor of VEGF acts as an important biomarker in psoriasis vulgaris and is histopathologically found in keratinocytes. The standard therapy of psoriasis vulgaris has been known to have good efficacies, but both long-term efficacy and treatment failures often occur, patients could not prevent relapse and serious side effects. Therapeutic agents that target VEGF directly including anti-VEGF monoclonal antibodies, VEGF receptor antagonist fusion proteins, receptor tyrosine kinase inhibitors, NVP-BAW2881, and traditional therapeutic agent PSORI-CM02. These therapies are quite promising, though there are various side effects associated with systemic administration of VEGF inhibitors, including proteinuria, hypertension and impaired wound healing. Thus, the development of anti-VEGF as a therapy in the management of psoriasis requires careful evaluation especially to minimize the toxicity of the treatment. Although these therapies appear to be promising, there are a number of side effects associated with systemic VEGF inhibitor use, including proteinuria, hypertension, and poor wound healing. Consequently, the development of anti-VEGF as a therapeutic in the treatment of psoriasis necessitates careful consideration, particularly to limit treatment toxicity.

Key words
Vascular endothelial growth factor; VEGF; Psoriasis vulgaris; Therapy; Angiogenesis.

Introduction

Incidence rates of the immune-mediated chronic skin disease psoriasis range from 1% to 3% worldwide.[1] Psoriasis vulgaris is characterized by erythematous and scaly plaques on the skin, especially on elbows, knees or elbows. scalp.[2] Management of psoriasis vulgaris still remains a challenge due to difficulties achieving target therapy.[3] Pathogenesis of psoriasis is influenced by T cells and skin vascular disorders play an important role. Angiogenesis in psoriasis is mediated by vascular endothelial growth factor (VEGF), angiopoietin, tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and interleukin-17 (IL-17).[1]

VEGFA inhibitors have not received approval in

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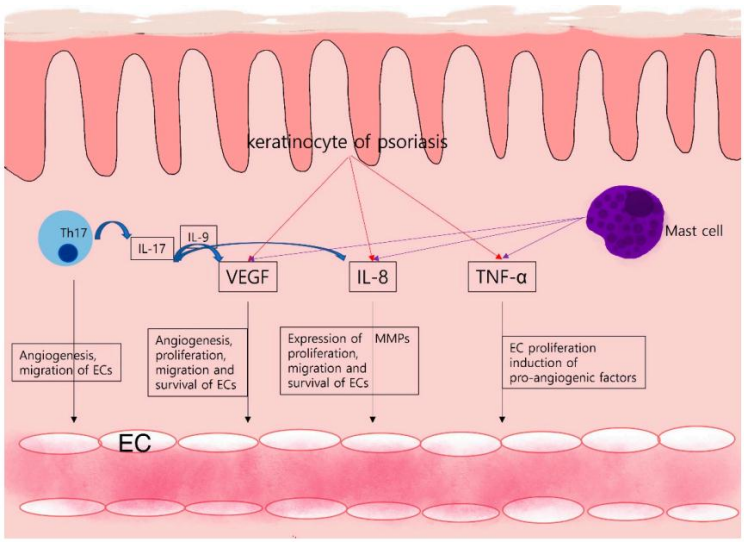

Figure 1 Angiogenesis in the pathogenesis of psoriasis.[1]

psoriasis therapy.[4] Gerkowicz *et al*., psoriasis therapy by targeting VEGF signaling by imiquimod and topical sunitinib, showed a decreased of inflammation.[5] This shows with appropriate therapy, psoriasis healing accompanied by normalization of the vascular structure has the potential to be achieved.[1]

Psoriasis is a chronic skin disorder with repeated remissions and relapses characterized by hyperproliferation of keratinocytes, inflammation and increased angiogenesis.[2,6] Prevalence of psoriasis are 0.5-11.4% cases in adult, and in Indonesia varies from 1.4% to 2.39%.[1,7,8] Relationship between genetic predisposition and inflammatory activity in psoriasis became clearer, susceptibility loci have been identified in T-cell activation or differentiation.[6,9–11]

Psoriatic skin cells cause increased angiogenesis by activating endothelial cells through pro-inflammatory cytokines, creating a link between the skin's abnormal epidermis and the disease's immunological component. Psoriasis relies heavily on VEGF as its primary angiogenesis mediator.[10,12] Pathologically elevated VEGF secretion by keratinocytes is caused by a number of causes, including genetic predisposition and pro-inflammatory cytokines released by leukocytes. Moreover, epidermal growth factor (EGF), transforming growth factor-1 (TGF-1), and tumor necrosis factor- (TNF-) all contribute to elevated VEGF levels **(Figure 1)**.[1,10]

Clinical manifestations of psoriatic lesions are well-defined erythematous psoriatic plaques covered with loosely adherent white or silver scales. Most common locations are scalp, chest, gluteus, and extremities.[7,13,14] PASI is an assessment to measure the severity of psoriasis based on erythema, induration, plaque thickness, and lesion extension based on BSA, classified as: mild (<10), moderate (10-20), and severe (>20).[15,16] Components of histopathological assessment on psoriasis vulgaris biopsy examination, include regular acanthosis, capillary dilation, and pathognomonic findings Munro's microabscesses and Kogoj's spongiform pustules.[9,17]

Several parameters must be considered in selecting psoriasis vulgaris therapy, the severity, location of skin lesions, patient risk factors, history of failed medications, functional, psychosocial limitations, the effectiveness and safety of each therapy. Less than 10% (mild psoriasis vulgaris), the chosen therapy is topical

Table 1 Failure of psoriasis therapy. [23]

Duration of Therapy	*Topical*	*Systemic*	*Biologic Agent*
3 months	17.0%	28.3%	45.4%
6 months	32.7%	46.3%	66.4%
1 year	49.0%	60.8%	80.2%
2 years	63.0%	73.5%	89.4%
3 years	70.7%	78.0%	93.6%

and can be combined with phototherapy. On a surface area of 10–30% (moderate psoriasis vulgaris), the preferred therapy is a combination of topical and phototherapy. Surface area >30% is necessary to give systemic therapy in combination with phototherapy and topical.[7] Moderate to severe psoriasis unresponsive to conventional therapies, the only treatment option available is biologic agents. Therapy with biologic agents tends to be expensive and long-term side effects that can be experienced are still not fully known.[14,18] Anti-IL-17 biologic agents (ixekizumab, secukinumab, brodalumab), anti-IL-12-23 inhibitors (ustekinumab), and anti-IL-23 inhibitors (guselkumab) are the most frequently used biologic agents in psoriasis vulgaris.[6] IL-37 can inhibit an overactive immune response as an immunosuppressive agent.[19]

Various advances in psoriasis therapy in an effort to increase patient efficacy, safety and compliance, still 85% of patients require better therapeutic modalities.[20] A treatment is considered successful if therapy can be stopped after achieving full clearance.[21] Patients tend to be non-compliant in continuing therapy due to ineffectiveness of the therapy being undertaken.[20] Treatment failure or long-term poorly tolerated therapy can result in ongoing inflammation and exacerbation of skin signs and symptoms, and comorbidities associated with psoriasis.[22] Systemic therapy generally fails more often due to side effects experienced, while biologic therapy is more likely to fail due to decreased therapeutic efficacy **(Table 1)**.[21,23] Targeted therapy has promising potential in the development of better therapeutic modalities in the hope of providing higher therapeutic success, and may have potential as a new alternative therapy in psoriasis.[5]

VEGF is a dimeric heparin-binding glycoprotein which in its active form is about 40 kDa. VEGF plays an important role in the process of angiogenesis, physiologically and pathologically.[24] Several VEGF subtypes are VEGFA, VEGFB, VEGFC, VEGFD, VEGFE, VEGFF, placental growth factor (PLGF), and endocrine gland–derived vascular endothelial growth factor (EG-VEGF) **(Figure 2)**.[4,25]

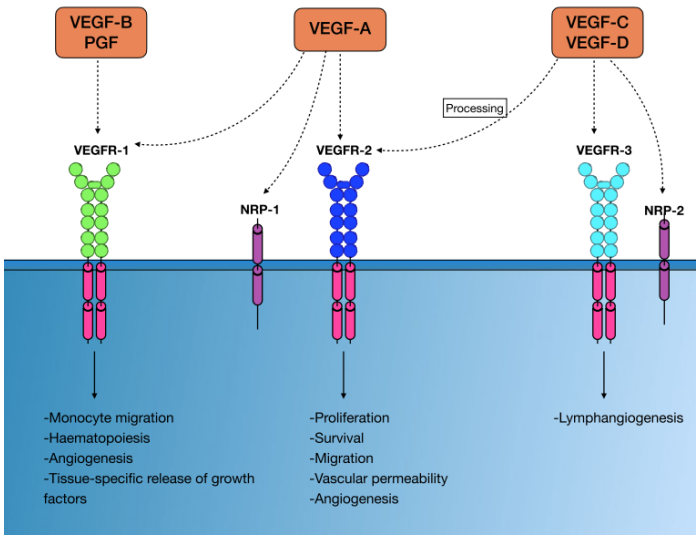

Figure 2 VEGF signaling and expression pathways. [4]

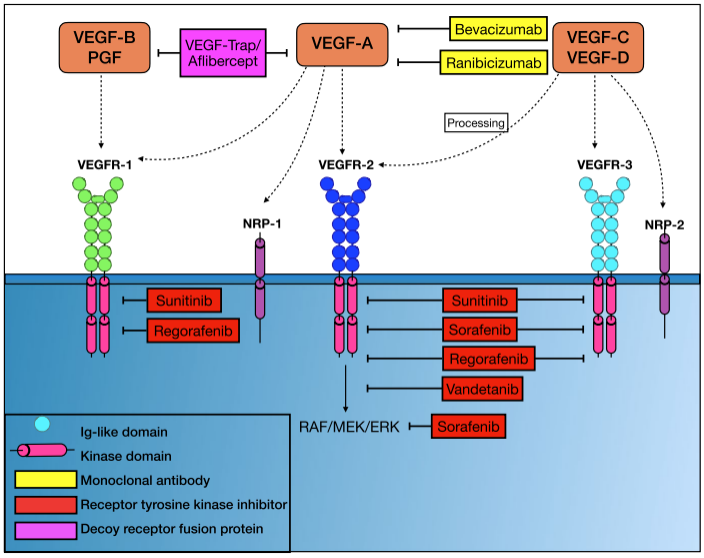

Figure 3 Mechanism of Action of VEGFA4 Inhibitors. [9]

Blood artery permeability can be raised by the growth factor VEGFA, also known as vascular endothelial growth factor. The mitotic activity of endothelial cells is specially stimulated by vascular endothelial growth factor (VEGF), which also raises vascular permeability and helps drive monocyte chemotaxis and activation.[12,26] VEGF ligand selectively binds to VEGF receptor (VEGFR) tyrosine kinase (TK), exerts its effects on vascular endothelium and peripheral monocytes.[5,12,26]Different cell types that express VEGF, include monocytes/ macrophages, keratinocytes, fibroblasts, osteoblasts, astrocytes, and tumor cells. VEGF expression is also influenced by proinflammatory cytokines, IL-8, IL-17A, TNF-α, basic fibroblast growth factor (bFGF), TGF-β, and prostaglandins.[5]

New blood vessels form from already present capillaries, a process known as angiogenesis. Angiogenesis is a process that involves the breakdown of the vascular basement membrane, the proliferation and migration of endothelial cells, the development of luminal structures, and the creation of new blood vessels. Endothelial cells, smooth muscle cells, and inflammatory cells are just a few of the cell types that play an important role in regulating the intricate process of angiogenesis. In response to physiological signals, vascular endothelial cells can divide, move, and differentiate quickly.[27]

Waworuntu *et al*., the median serum VEGF was 270,60 pg/mL. There was male preponderance, with the highest frequency in the age 40-60 years.[28] Different strategies targeting the VEGFA/VEGFR signaling system **(Figure 3)**, including:

1. Mechanism of direct neutralization of VEGFA via monoclonal antibodies

2. Inhibition of VEGFA receptor function with VEGF receptor tyrosine kinase inhibitors

3. Prevention of binding of VEGFA to its receptors.[4]

Based on a study conducted by Sankar *et al*.,[29] histopathologically, VEGF expression was found in all cases of psoriasis with various intensities **(Figure 4)**.[30]

Anti-VEGF monoclonal antibodies (bevacizumab) and VEGF receptor protein

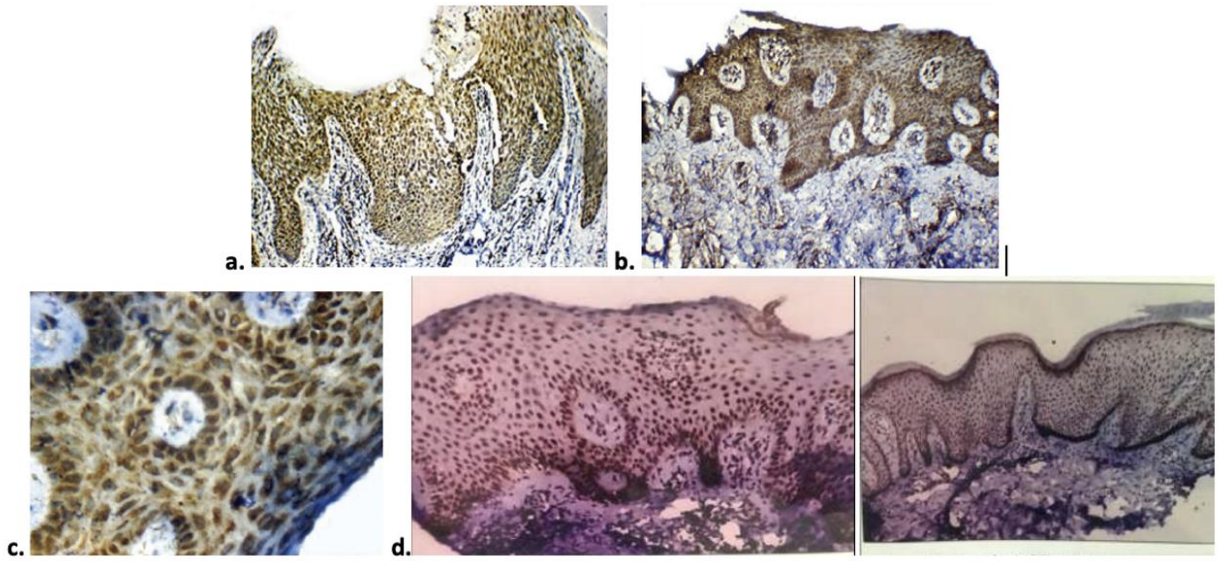

Figure 4 Histopathological expression of VEGF in patients with psoriasis: a. Moderate degree of epidermal positivity (2+), IHC 10x magnification; b. Diffuse epidermal positivity (3+), IHC 10x magnification; c. Cytoplasmic and epidermal membrane positivity (3+), IHC 40x magnification; d. Cytoplasmic positivity on epidermal basement and suprabasal membranes, IHC 400x magnification. [29,30]

antagonists are examples of therapeutic medicines that target VEGF directly (Aflibercept, Pegaptanib and Valpha). Small-molecule inhibitors of VEGFR tyrosine kinase activity are examples of agents that suppress VEGF signaling (Sunitinib, Sorafenib, and NVP-BAW2881).[12]

1. Anti-VEGF monoclonal antibodies

a. Bevacizumab

Bevacizumab is generally given intravenously 5 to 15 mg/kg.[31] The recombinant monoclonal antibody bevacizumab works by blocking the binding of VEGFA to its receptors. It does this by binding to all circulating VEGFA isoforms.[4] Bevacizumab treatment resulted in dramatic improvements in two reported cases of psoriasis.[4] Side effects of bevacizumab administration include gastrointestinal perforation, bleeding, severe hypertension, and impaired wound healing.[12]

b. G6-31

Administration of G6-31 injection to rats resulted in almost complete and moderate remission of skin inflammation, scales, and edema. Epidermal structure normalized with significant reduction of psoriasis-like features. The narrowing of blood arteries and lymphatic vessels is being corrected in a procedure called vascular reconstruction. There was a marked drop in the number of blood vessels as well.[12]

c. Ranibizumab

Ranibizumab is a monoclonal antibody fragment derived from bevacizumab. Its primary purpose is the treatment of macular degeneration, macular edema caused by retinal vascular blockage, and diabetic retinopathy. Vasculogenesis can be stifled thanks to ranibizumab's high-affinity binding to the VEGF receptor.[12]

2. VEGF Receptor Antagonist Fusion Protein

a. Aflibercept

Aflibercept is a fusion protein with binding to VEGFR1 and VEGFR2. This agent acts as a decoy receptor that binds irreversibly to VEGFA, VEGFB, and PLGF. Side effects include hypertension, proteinuria, fatigue, pulmonary hemorrhage, and lymphopenia.[4,12]

b. Valpha

Valpha is a novel chimeric fusion protein that can inhibit TNF-α and VEGF, and consists of four cysteine-high domains of the TNF-α TNFR2 receptor that are joined to the Ig-like domain 2 of VEGFR1 that binds to human Fc IgG.[12]

c. Pegaptinib

Pegaptanib sodium is a single-stranded nucleic acid with PEG that binds to the VEGF165 receptor.[32]

3. Receptor tyrosine kinase inhibitors

a. Sunitinib

Sunitinib is a tiny drug that inhibits the tyrosine kinase domain of vascular endothelial growth factor receptor. Sunitinib therapy for renal cell carcinoma improved chronic psoriasis vulgaris in two reported cases. Common side effects include diarrhea, mucositis/stomatitis, hypertension, hand-foot syndrome and fatigue.[12]

b. Sorafenib

Sorafenib is a multikinase inhibitor that acts on the VEGFR tyrosine kinase domain and can be administered topically. The side effects are hand-foot syndrome, diarrhea, fatigue, alopecia, and hypertension.[12]

c. NVP-BAW2881

The tyrosine kinase domain of VEGF receptor 2 is the intended target of NVP-BAW2881. In nanomolar concentrations, these drugs have been demonstrated to impede endothelial tube formation and decrease proliferation and migration of endothelial cells.[26]

4. PSORI-CM02

PSORI-CM02, is a traditional Chinese medicine which shows a safe and effective treatment of psoriasis. It significantly inhibited IL-17A-stimulated HUVEC proliferation and migration.[33]

Vascular dysfunction, i.e., VEGFA/VEGFR-influenced angiogenesis abnormalities in the papillary layer of the dermis of psoriatic lesions, not only has a significant role in the entire pathogenesis of psoriasis, but can also be a promising therapeutic target to provide long-term beneficial effects in the management of psoriasis in future.[4]

Conclusion

VEGF plays a crucial role in the pathophysiology of psoriasis through its mediation of angiogenesis. The angiogenic factor of VEGF acts as an important biomarker in psoriasis vulgaris and is histopathologically found in keratinocytes. Although various therapies have been known to have good efficacies in the treatment of psoriasis, long-term efficacy and treatment failure often occur, patients cannot prevent relapse and serious side effects occur. Therapeutic agents that target VEGF directly include anti-VEGF monoclonal antibodies (bevacizumab, G6-31, and ranibizumab); VEGF receptor antagonist fusion proteins (aflibercept, valpha, and pegaptinib); receptor tyrosine kinase inhibitors (sunitinib, sorafenib, and NVP-BAW2881); proteinuria, hypertension, and poor wound healing are some

of the side effects of systemic administration of VEGF inhibitors, which are common with the standard therapeutic drug PSORI-CM02. Hence, anti-VEGF therapeutic development in the management of psoriasis necessitates cautious assessment, particularly to lessen treatment-related side effects.

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