POTENTIAL USEFULNESS OF SERUM ANGIOPOIETIN-2 AS A BIOMARKER OF PSORIASIS VULGARIS

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ABSTRACT

Background: Psoriasis vulgaris is a multifactorial immune-mediated disease affect the skin, hair, nail and joint, with severe impact on quality of the patient life. Pathogenesis of psoriasis is complex and the exact mechanism is not fully understood. The disease is thought to result from a combination of genetic and environmental factors. Psoriasis affect primarily the skin and/or joints and is characterized by immune pathological inflammation, angiogenesis and keratinocyte hyper proliferation. These changes are believed to stem from the premature maturation of keratinocytes induced by an inflammatory cascade in the dermis involving dendritic cells, macrophages and T cells. Angiopoietins (Ang-1 and Ang-2) are endogenous glycoprotein that in humans is encoded by the ANGPT2 gene, their binding to tyrosine kinase receptor (Tie-2) is crucial to angiogenesis process. Paracrine Ang-1-mediated activation of Tie-2 acts as a regulator of vessel maturation and vascular quiescence turn, the antagonistic ligand Ang-2 acts by an autocrine mechanism and expressed only at the sites of vascular remodeling similar to angiopoietin-1. Transgenic over expression of ANGPT2 disrupt blood vessel formation.

Key words: Psoriasis Vulgaris, Angiopoietin-2.

I. PSORIASIS:

Psoriasis is a common chronic inflammatory, immune-mediated skin disorder and is characterized by variably sized, well-demarcated, dry plaques usually covered with layers of fine, silvery scales. With a spectrum of clinical phenotypes and results from the interplay of genetic, environmental and immunological factors. In combination with skin barrier disruption (1).

Epidemiology

Psoriasis affect approximately 0.5%–1% of children and 2%–3% of the world’s population. The rate of psoriasis varies according to age, region and ethnicity; a combination of environmental and genetic factors is thought to be responsible for these differences. It is a bi-modally distributed disease (with one major age of onset at 20–30 years of age as well as a later smaller peak of onset at 50–60 years) and affect both sexes equally (2).

Classification of Psoriasis

Classification proposed by the International Psoriasis Council, which identifies four main forms of psoriasis: plaque-type, guttate, GPP, and erythroderma, and several further subphenotypes according to distribution (localized vs. widespread), anatomical localization (flexural, scalp, palms/soles/nail), size (large vs. small) and thickness (thick vs. thin) of plaques, onset (early vs. late), and disease activity (active vs. stable) (9).
A further classification takes into account the age of onset. Type I psoriasis has early onset (<40 yr), is often associated with familiar disease history and shows high association with the human leukocyte antigen (HLA)-Cw0602 allele, whereas type II psoriasis develops after the age of 40 (Henseler and Christophers 1985). In addition to important distinctions such as pustular and non-pustular psoriasis (Table 1).

**Table (1): Clinical forms of non-pustular and pustular psoriasis (3).**

<table>
<thead>
<tr>
<th>Non-pustular psoriasis</th>
<th>Pustular psoriasis</th>
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<tbody>
<tr>
<td>Psoriasis vulgaris (early and late onset)</td>
<td>Generalized pustular psoriasis</td>
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<tr>
<td>Guttate psoriasis</td>
<td>von Zumbusch type</td>
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<tr>
<td>Erythrodermic psoriasis</td>
<td>Impetigo herpetiformis</td>
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<tr>
<td>Palmoplantar psoriasis</td>
<td>Localized pustular psoriasis</td>
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<td>Psoriatic arthritis (PsA)</td>
<td>Palmoplantar pustular psoriasis (Barber type)</td>
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<tr>
<td>Drug-induced psoriasis</td>
<td>Acrodermatitis continua of Hallopeau</td>
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<td>Annular pustular psoriasis</td>
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Psoriasis vulgaris (also known as chronic stationary psoriasis or plaque-like psoriasis) is the most common form and affects 85%–90% of people with psoriasis. Characterized by oval or irregularly shaped, red, sharply demarcated and raised plaques covered by silvery scales. Plaques occur mainly on the extensor surface of elbows and knees, on the scalp, umbilicus and in the lower back, but can affect every area of the body, often with a symmetrical distribution (figure 1). Size of the lesions can vary from pinpoint to larger individual lesions or confluent areas. White blanching ring, known as Woronoff’s ring, may be observed in the skin surrounding a psoriatic plaque. With gradual peripheral extension, plaques may develop different configurations including: psoriasis gyrate in which curved linear patterns predominate. Annular psoriasis in which ring-like lesions develop secondary to central clearing (4).

![Figure (1): Symmetrical distribution of typical well-demarcated erythematous plaques covered by silvery lamellar scales on the back and elbows of a patient (5).](image)

**Histological Manifestation**

In the early stages of a newly developing plaque, the first changes occur in the uppermost layer of the dermis, the papillary dermis. Blood vessels become dilated and tortuous, with lymphocytes and neutrophils emerging from their lumen (“squirting” papilla) and reaching for the epidermis, which looks still quite normal at this stage. These vessels are contorted and elongated, spreading along the extended papillary dermal region between the outstretched epidermal rete ridges. These changes explain the visible redness of the psoriatic lesions (6).
Regarding the molecular level, the endothelial cells are activated, as demonstrated by their increased staining for molecules such as CD54, CD106, and P-selectin, which facilitates the continuous immigration of immune cells into the skin tissue. Shortly after, aberrant keratinocyte (KC) proliferation and migration begin, resulting in epidermal thickening, incomplete terminal differentiation with initial loss of the “stratum granulosum,” and the appearance of foci of parakeratosis (retention of the nucleus by corneocytes) (7).

In the advanced stage, fully flagged psoriasis hyperplasia is present with acanthosis and papillomatosis with elongation of the rete ridges extending downward between dermal papillae. Parakeratosis becomes confluent, the stratum granulosum is absent, lymphocytes, mainly CD8+ T cells, are interspersed between KCs, and neutrophils accumulate into the parakeratotic scales, forming Munro micro abscesses (figure3). The dilated blood vessels extend high into papillae, accounting for pinpoint bleeding when a scale is removed, known as Auspitz sign (8).

The dermis is heavily infiltrated by T cells and dendritic cells (DC). Resolving lesions after therapy can be encased by a distinctive rim of blanching (Woronoff’s ring), predictive of clearing and histologically characterized by orthokeratosis, that is thickening of the stratum corneum without parakeratosis and restoration of the stratum granulosum (9).

II. ACTIVATORS OF INFLAMMATION IN PSORIASIS

A. Cytokines

- **IL-23**

IL-23 has importance in maintaining the cytokine milieu required for the survival of Th-17 cells. Naive T-cells do not express IL-23R and therefore cannot be directly activated by IL-23. In the presence of a combination of cytokines naive T-cells differentiate into Th-17 cells. Studies showed that increased levels of IL-23 in psoriatic skin compared to non-lesioned skin (10).

- **IL-1β**

Since IL-1β is a well-known initiator and effector for inflammation, several proteins involved in the production of this interleukin in psoriasis were investigated. CCN1 (cysteine-rich protein 61), a protein involved in inflammation, cell proliferation and angiogenesis, among others, was shown to be upregulated in psoriasis skin lesions and to promote keratinocyte proliferation and was also shown to increase the production of IL-1β. This suggests that CCN1 plays a role in psoriasis pathogenesis and modulating inflammation in the disease (11).

- **IL-17**

Previous studies showed that IL-17 levels are increased in psoriatic patients and the role of the interleukin in psoriasis is further supported by the favorable results obtained with biological agents targeting IL-17 (12). Even though IL-17A and IL-17F are the most important of the IL-17 family members involved in the pathogenesis of psoriasis, IL-17E is also increased in keratinocytes from the psoriasis plaque and seems to play a proinflammatory role, as it is implicated in macrophage activation (13). IL-17 has also been linked to cardiovascular disease and other inflammatory comorbidities. (14).

- **IL-22**

IL-22 is involved in enhancing keratinocyte migration, increasing epidermal thickness by interfering with physiological desquamation, producing chemokines, AMPs, neutrophil chemotactants and inducing production of MMPs (15).

- **IFN-γ**

Involved in innate and adaptive immunity. High levels of IFN-γ mRNA were identified in psoriasis lesions and psoriatic blood. There is a correlation between IFN-γ levels and disease severity measured by PASI. However, in a study used a neutralizing anti-IFN-γ antibody in treatment had minimal efficacy and concluded that IFN-γ is not a major pathogenic cytokine in psoriasis lesions (16).

- **T-Cells**
• **Th-17 Cells, Th-22 Cells**

Increased levels of Th-22, as well as Th-17, were identified in psoriasis vulgaris and psoriatic arthritis. Study showed that epidermal Th-22 and Tc-17 are retained in healed psoriasis and can produce cytokines involved in psoriasis pathogenesis, thus promoting disease recurrence in previously affected areas (17).

• **Th-1 Cells**

IL-12 determines the differentiation of naive Th cells into Th-1 cells and enhances the production of IFN-γ. While Th-17 cells play an important role in the initiation phase of the disease, Th-1 cells/IFN-γ-associated inflammation predominate in chronic plaques (17).

B. **Regulatory Axis in Psoriasis**

• **Treg Cells**

Treg cells are a heterogenous group of T lymphocytes responsible for suppressing an excessive or auto reactive immune response, thus playing an important role in immunological tolerance. Abnormalities in Treg cells have been associated with inflammation in psoriasis. some authors found lower levels of Treg cells in the peripheral blood of psoriatic patients and skin samples (18).

![Image](https://example.com/image.png)

**Figure (2):** Role of CD4 T cell subtypes in psoriasis. Pro-inflammatory cytokines produced from Th1 and Th17 dominate the cytokine profile in psoriasis (18).

They mediate keratinocyte hyperproliferation and trigger a ‘vicious cycle’ of inflammation. IL-23 released by psoriatic keratinocytes and sentinel cells such as dendritic cells and macrophages, is critical for maintenance of Th17 function. Low levels of anti-inflammatory cytokines released by Th2 and Treg cells potentially counteract but cannot balance the effects of Th1/Th17 cytokines. Green arrows denote stimulatory actions; red blocking lines denote inhibitory action

• **TGFβ**

TGFβ is a multipotent growth factor involved in maintaining immune homeostasis. It inhibits the activity of macrophages and neutrophils, promotes angiogenesis and the proliferation of fibroblasts and regulates T cells subpopulations. TGFβ-1 was considered an anti-inflammatory cytokine. However, its overexpression in keratinocytes was shown to induce skin inflammation and the development of psoriasis-like lesions. In patients with psoriasis, TGFβ-1 induces the generation of FOXP3 positive Treg cells in the absence of IL-6 and the production of Th-17 cells in the presence of IL-6. While the exact role of TGF-β in the pathogenesis of psoriasis is not completely understood, data available suggests that it might be a good biomarker for the severity of psoriasis (19).
• **IL-10**

IL-10 is one of the most potent anti-inflammatory cytokines. Macrophages are the most important source of IL-10, but it is also secreted by (B cells, T cells, mast cells, dendritic cells, keratinocytes, eosinophils and NK cells). IL-10 performs its regulatory actions through the modulation of antigen presentation in dendritic cells, suppression of T cell activity and stimulation of B cell differentiation. Studies performed in patients with psoriasis showed that the levels of IL-10 are decreased in the patients’ serum. Various psoriasis treatments have been associated with an increase in the levels of IL-10 (20).

### III. EVALUATION OF DISEASE SEVERITY

The assessment of disease severity in psoriasis patients serves different goals: to assess the burden of disease as objectively as possible, determine the indication for treatment especially systemic therapy and evaluate treatment response and possibly the need for adjustment.

#### Assessment of skin involvement

Currently the gold standard score for the assessment of extensive psoriasis is **PASI score**. It is present a scoring system that ranges from 0 to 72 points. Here, both the severity and extent of the disease are calculated separately for four body regions: head (h), upper limb (u), trunk (t) and lower limbs (l). PASI measures erythema, induration, and scaling on a five-point-scale ranging from 0 (no symptoms) to 4 (very severe symptoms) for each criterion. The area is assessed depending on the involvement of the specific region; 0 to 6 points are attributed: 1 = 1–9%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, and 6 = 90–100%. To account for the difference in body surface involvement as a proportion of the whole integument, a factor is applied, ranging from 0.1 to 0.4 for the head, the upper extremities, the trunk, and the lower extremities.

The final formula for PASI score is $\text{PASI} = 0.1 \times (\text{Eh} + \text{Ih} + \text{Dh}) \times \text{Ah} + 0.2 \times (\text{Eu} + \text{Iu} + \text{Du}) \times \text{Au} + 0.3 \times (\text{Et} + \text{It} + \text{Dt}) \times \text{At} + 0.4 \times (\text{El} + \text{Il} + \text{Dl}) \times \text{Al}$.

PASI enables a historical comparison between different clinical trials and remains the best-evaluated objective method to define disease severity in plaque psoriasis. Despite limitations such as its low response in mild disease, or its complexity and lack of consensus on interpretability, the PASI remains the best-studied and evaluated scoring system.

#### Angiopoietin-2

Since the discovery of the angiopoietins, much interest has been focused on their biological actions and their potential use as therapeutic targets. It is generally accepted that the angiopoietins play an important role in angiogenesis and hence are described as angiogenic factors. However, it is becoming increasingly clear that this is not their only role, and it is likely that the angiopoietins have important roles in a wider range of biological and pathological functions (20).

The angiopoietins (Ang) are endogenously secreted glycoproteins. They were identified via secretion trap and homology cloning techniques as a family of structurally related proteins that bind with similar specificity and affinity to a common endothelial cell-specific receptor tyrosine kinase, Tie2. The family comprises three structurally related proteins, termed Ang-1, Ang-2, and Ang-3/4. The most striking feature of this family is the opposing effects of these ligands binding to the receptor.

Ang-1 elicits an activation of Tie2, seen by increased tyrosine phosphorylation of Tie2. Ang-2 appears to inhibit receptor activation and can even specifically block the Ang-1 dependent phosphorylation (21).

Angiopoietin-3 represents the murine orthologue of human Ang-4, although, these ligands themselves show opposing effects on the receptor. Ang-4 showing activation and Ang-3 showing inhibition of receptor activation. The ability of Tie2 to distinguish between Ang-1 and Ang-2 appears to be dependent on the context of the receptor. Tie2-transfected fibroblasts, which do not normally express this protein, show receptor phosphorylation in response to both Ang-1 and Ang-2 (22).

Hence Ang-2 has both agonistic and antagonistic properties depending on the environment of its receptor. These effects of the Ang suggest that Tie2, through which intracellular signalling mechanisms are activated, must have cellular actions that require very precise regulation and raise interesting questions as to its biological functions (23).
IV. REGULATION OF THE ANGIOPOIETINS EXPRESSION

The mechanisms by which regulation of expression of the Ang occurs are not clear. Ang-2 expression in a variety of systems has been reported to be up-regulated by:

A. Hypoxia: Angiopoietin-2 mRNA and protein levels in endothelial cells are induced by hypoxia. The level of induction varies from two- to six-fold depending on the particular endothelial cell line and culture conditions. This increase in mRNA level is due to increased transcription rather than increased mRNA stability. The effect of hypoxia on the expression levels of Ang-2 is dependent on the cell type. For example in renal clear cell carcinoma cells (RCC) in vitro express a relatively high level of Ang -2, which is down-regulated under hypoxic conditions. The effect of hypoxia on Ang -2 expression in RCC is opposite to that seen in endothelial cells, suggesting that individual cell types may have specific regulatory mechanisms controlling the expression of some, if not all, angiogenic factors (24).

B. Hypoxia inducible factor 1α: It was finding that HIF-1α is upregulated in the skin of psoriatic cases (involved and uninvolved) compared to normal skin indicate its role in pathogenesis of psoriasis especially its active nuclear form that show an association with angiogenesis and proliferation (25).

C. VEGF: Is reported to increase Ang-1 expression in retinal pigment epithelial cells Steroidal hormones: Play a role in the regulation of angiogenesis and many endothelial cells have been shown to express oestrogen receptors. Oestrogen has been shown to induce Ang-2 levels approximately two-fold in non-reproductive tissues. Complete characterization of the promoter regions is needed in order to determine whether oestrogen has a direct effect on Ang expression levels, while testosterone has been shown to have no effect on the expression levels of either Ang -1 or Ang -2 in prostate cells (26).

Down-regulated by basic fibroblast growth factor (FGF) and von Hippel–Lindau gene. Von Hippel–Lindau gene Cause reduction in Ang -2 mRNA and regulates the activity of HIF-1α. The effect of TNFα on Ang expression levels in vitro is less clear, but it was finding that TNFα exert regulatory effects on Ang -2 expression levels. In contrast, very little is known about the regulation of Ang-1 expression (27).

Given the number of instances where Ang-2 expression levels have been shown to be up-or down-regulated, there is little information incoming for Ang -1. Since many laboratories have looked at the levels of both Ang -1 and Ang -2 during their studies, presumably there is little variation in the level of expression of Ang -1 (28).

This suggests that Ang -1 expression may be driven from a promoter that is not subject to much regulation. However, expression levels of Ang -2 show greater fluctuation, even though these are often only two-fold differences. This suggests that the Ang -2 promoter might be sensitive to a number of regulatory processes (29).

Angiopoietin-2 in Psoriasis

Psoriasis lies at the crossroads linking the pathways of angiogenesis and inflammation. Mediators such as angiopoietin-2 play significant roles in the pathophysiology and may even account for the maintenance of the chronic inflammatory state. Furthermore, certain polymorphisms in the gene encoding Ang2 are associated with increased risk of psoriasis vulgaris (PsV). Thus, the critical role of this signaling system in psoriasis pathogenesis is strongly suggested, but there has been no report regarding serum Ang2 levels in this disease (30).

Dysregulated angiogenesis has been observed in inflammatory diseases and might underly chronic cutaneous inflammation in psoriasis. The redness of the psoriatic lesions is due to increased numbers of tortuous capillaries that reach the skin surface through a markedly thinned epithelium. The formation of new blood vessels starts with early psoriatic changes and disappear with disease clearance (31).

Several other studies have demonstrated that these microvascular changes occur early in the development of the psoriatic lesions. Histological examination of biopsies taken from lesions which are just detectable clinically reveals a normal epidermis but dilated and abnormally orientated capillaries in the papillary dermis. When the advancing edge of psoriatic tissue is predicted by tracking the growth of an expanding plaque laser doppler fluxmetry indicates an increase in cutaneous blood flow in perilesional, clinically normal skin whereas immune-histological parameters of epidermal proliferation and leukocyte accumulation in this skin remain unaltered (32).
V. PRO-ANGIOGENIC FACTORS IN PSORIATIC SKIN

Since vascular proliferation occurs only in the presence of an appropriate stimulus, several studies have attempted to demonstrate pro-angiogenic activity within psoriatic skin.

Detailed search for the pro-angiogenic mediator revealed a large spectrum of keratinocyte-derived pro-angiogenic factors, including VEGF, HIFs, angiopoietins, pro-angiogenic cytokines, such as tumor necrosis factor α (TNFα), TGF-α, interleukin (IL)-8 and IL-17, are involved in psoriasis development and pathogenesis. Also, expression levels of these molecules are reversed in parallel with the resolution of psoriatic lesions (35).

Already in uninvolved, non-lesional skin significant over-expression of several VEGF isoforms was observed in patients as compared to healthy skin of normal volunteers. These findings suggest that angiogenesis is also one of the key features in the pathogenesis of psoriasis and various studies focused on the identification and role of pro-angiogenic mediators in psoriatic skin (36).

Vascular endothelial growth factor (VEGF) is a homodimeric protein produced predominately by keratinocytes, and to a far lesser extent by fibroblasts that acts as a potent and selective mitogen for endothelial cells. Studies have shown increased VEGF mRNA in lesional psoriatic keratinocytes and a direct relation between severity of disease
and VEGF production. Experiments on transgenic mouse models have demonstrated that induced overexpression of VEGF by basal keratinocytes resulted in an expanded superficial dermal microvasculature similar to that seen in psoriatic skin. VEGF not only promotes angiogenesis but also enhances vascular permeability, as elevated plasma levels of VEGF are found in patients with erythrodermic psoriasis. It stimulates secretion of interstitial collagenase, thereby suggesting a synergistic role with ESAF in the expansion of the microvasculature in psoriatic plaques (37).

Endothelial cell stimulating angiogenesis factor (ESAF) is a nonenzymatic, non-proteinaceous angiogenic mediator produced in approximately equal amounts by keratinocytes and fibroblasts, which stimulates proliferation of microvascular endothelial cells and pericytes in vitro. ESAF is significantly elevated in lesional skin and in serum of patients with psoriasis. Moreover, ESAF, apart from its direct mitogenic effects on endothelial cells, is also able to activate the three major matrix metalloproteinases which are involved in angiogenesis in vitro (38).

Tumor necrosis factor-α is a cytokine produced by keratinocytes and endothelial cells that upregulates expression of some pro-angiogenic factors, such as VEGF, angiopoietin 2, Tie-2 receptor (tyrosine kinase with immunoglobulin-like loop and EGF homology domains) as well as intercellular/vascular cell adhesion molecules involved in trafficking of lymphocytes to inflammatory lesions. Expression of TNF-α is elevated in psoriatic skin (39).

Transforming growth factor-α is a cytokine with angiogenic properties. Some authors demonstrated an overexpression of TGF-α in psoriatic epidermis compared with uninvolved skin. It was found, using RNA hybridization techniques, that involved epidermis had a fourfold increase in TGF-α mRNA and a six fold increase in TGF-α protein compared with uninvolved skin. These findings underline the importance of TGF-α in the development of psoriatic vascular changes (40).

Platelet derived epidermal growth factor is a molecule secreted by platelets, macrophages, endothelial cells, fibroblasts, and keratinocytes, which is currently considered to be one of the most potent angiogenesis inducers. It is overexpressed in psoriatic skin (41).

Angiopoietins are produced by mesenchymal cells and are expressed at sites of blood vessel proliferation and remodeling in psoriatic skin. They seem to have complementary and co-ordinated roles with vascular development in association with VEGF. Ang-2 expression can be upregulated by VEGF, bFGF and hypoxia and can be down-regulated by Ang-1 and TGF-β. Kuroda et al, (35) examined the potential role of angiopoietins and Tie2 receptor in psoriasis. Their studies demonstrated that Ang 1 and 2 and Tie2 were up regulated in lesional skin in psoriasis compared with non-lesional, psoriatic skin, healthy skin and chronic dermatitis skin.

Ang 1 was expressed by stromal cells in the vascualrised papillary dermis of lesional skin, whereas Ang 2 was expressed by endothelial cells in the vicinity of VEGF-expressing epidermal keratinocytes. In addition VEGF and basic FGF, which were overexpressed in lesional psoriasis skin, enhanced Ang 2 and Tie2 expression in dermal micro vascular endothelial cell cultures.

Kuroda et al, (35) concluded that up regulation of Ang 1, Ang 2 and Tie2 is closely associated with the development of micro vascular proliferation in psoriasis, and that the angiopoietin-Tie2 system may act co-ordinately with VEGF and bFGF to promote angiogenesis in psoriasis.

Other evidence which supports that angiogenesis are seen in psoriasis are the following: Enhanced blood flow in psoriasis skin biopsy using laser doppler fluxmetry, increased microvasculature in the psoriatic skin lesion seen in autoradiograph, the ultrastructural studies which show tortuous and elongated capillary loops in lesional psoriatic skin.
VI. CLINICAL TRIALS FOR ANTIANGIOGENESIS

Traditionally, psoriasis therapies have focused on treating epidermal hyperplasia that result from abnormal proliferation and differentiation of basal keratinocytes. Novel therapeutic interventions have focused on angiogenic pathway modulation. Evaluation of microcirculation modifications in lesional skin serves to assess the efficacy of new therapies. Drugs used in psoriasis may have antiangiogenic properties. Methotrexate was once the most popular systemic drug against psoriasis, and has been demonstrated to have antiangiogenic properties. Other compounds used against psoriasis, including cyclosporine, retinoids, and vitamin D analogs have also been shown to have antiangiogenic properties (43).

Coal tar, one of the oldest remedies for psoriasis, has been shown to induce long term remissions in psoriasis. Coal tar was founded as an angiogenic inhibitor, carbazole, which blocks rac-stat3 function and may account for the therapeutic activity of coal tar in psoriasis, as well as block production of interleukin-15. Razoxane, an anti-mitotic drug, has been shown to have an effect on tumor vascular supply. It has biological similarity to An-2. Razoxane is associated with an increased risk of acute myeloid leukemia subsequent to prolonged use, which led to its withdrawal as a viable treatment for psoriasis. However, there has been renewed interest in the anti-angiogenetic effects of razoxane on human tumors (44).

Treatment with pulsed dye laser has been associated with significant reduction of the density and length of cutaneous microvessels and with clinical improvement. Antimicrobial peptides which are overexpressed in psoriasis stimulate generation of reactive oxygen. Thus, it is likely that psoriasis represents a reactive oxygen driven process, and that inhibitors of this process may be beneficial in the treatment of angiogenesis associated with psoriasis (45).

At present, inhibitors of the VEGF pathway are the most clinically advanced, and bevacizumab, a humanized variant of a murine anti-VEGF-A monoclonal antibody that was used in early proof-of-concept studies, is the only FDA-approved antiangiogenic treatment for cancer therapy. Anti-VEGF antibody treatment in psoriasis mouse models results in clinical improvement of psoriasiform disease. Furthermore, psoriasis patients treated with anti-VEGF therapies for cancer such as bevacizumab have shown complete clearance of their disease. Tie2 transgenic mice, which have over expression of Tie2, the receptor for angiopoietin-1 and -2, also display psoriasiform skin inflammation. Thus, neutralizing antibodies and soluble receptors to angiopoietins such as VEGF, fibroblast growth factor-2 and angiopoetin-1 and -2 may have a therapeutic benefit in psoriasis. AE-941 (Neovastat; Aeterna

www.turkjphysiotherrehabil.org
Laboratories) is a naturally occurring inhibitor of angiogenesis derived from shark cartilage, which inhibits both VEGF and matrix metalloproteinase, activators of angiogenesis (46).

Conflict of Interest: No conflict of interest.

REFERENCES


