INTRODUCTION

Psoriasis is a chronic, immune-mediated hyperproliferative skin disease that affects 1%-3% of the population.[1] Genetic and environmental factors play important roles in the pathogenesis of psoriasis, which is characterised by abnormal keratinocyte proliferation and differentiation, infiltration of immune cells and increased vascularity in the papillary dermis.[2-5] (Figure 1A). In spite of psoriasis being a mostly T-cell–driven disease,[6] the pathophysiology of psoriasis is highly modulated by abnormalities in the vasculature in the papillary dermis. Yet, these are not specifically targeted by the current standard-of-care in psoriasis management.[1,7] In fact, to date, most psoriasis research has focused on the immune component of the disease while the vascular contribution to psoriasis pathogenesis and maintenance has received...
much less attention. The current viewpoint essay therefore refocuses attention on the underestimated role of the vasculature in psoriasis. Vascular endothelial growth factor-A (VEGF-A) is recognised not only as the main angiogenic mediator, but also as a key mediator of angiogenesis in pathological processes including solid tumors and intraocular neovascular syndromes. VEGF-A is now appreciated to play a critical role in the pathogenesis of several inflammatory immune-mediated diseases including psoriasis (see below).

**FIGURE 1** Histological hallmarks of psoriasis and the Auspitz sign. A, Plaques of psoriasis are characterised by (1) epidermal hyperplasia and keratinocyte hyperproliferation that leads to elongation of the rete ridges and epidermal thickening (hyperkeratosis). The keratinocytes in plaques of psoriasis proliferate rapidly and differentiate from the stratum basale of the epidermis to the stratum corneum eight times faster than keratinocytes in healthy skin. (2) The shortened epidermal turnover leads to incomplete keratinocyte differentiation and retention of nuclei by the keratinocytes in the stratum corneum (parakeratosis). (3) Moreover, the granular layer of the epidermis, where terminal keratinocyte differentiation begins, is reduced or missing in plaques of psoriasis leading to supra-papillary epidermal thinning. (4) Munro's microabscesses are associations of IL-17 expressing neutrophils that can be present in plaques of psoriasis. (5) The blood vessels in the papillary dermis of plaques of psoriasis are elongated, dilated and more tortuous compared to the blood vessels in healthy skin. (6) The inflammatory cell infiltration in plaques of psoriasis includes T cells, neutrophils, dendritic cells, macrophages and mast cells. (7) The lymphatic vessels in plaques of psoriasis are dysfunctional, tortuous and dilated. B, Plaque of psoriasis covered by white scales. Psoriasis characteristically affects the extensor aspects of the limbs; the image shows a plaque present in the knee of a patient with plaque psoriasis. The microvascular changes in the papillary dermis of plaques of psoriasis are clinically evident because they lead to the redness appearance. C, Removal of the scales in a plaque of psoriasis leads to the appearance of small bleeding points (yellow arrows), a characteristic feature of psoriasis termed the Auspitz sign. 

(A) Healthy skin  
(B) Plaque of psoriasis  
(C) Removal of scales
Therefore, we discuss here the concept that VEGF-A-mediated angiogenesis plays an important role in the development of lesions of psoriasis. We then focus on discussing the hypothesis that VEGF-A and signalling through its receptors constitute a promising target for therapeutic intervention in the future management of psoriasis, for example via VEGF-A blockade with clinically available monoclonal antibodies.\[17,18\] We develop the line of argumentation that supports this hypothesis and argue that this treatment strategy expands and optimises therapeutic options for a personalised medicine approach in the future management of psoriasis.\[17,18\]

2 | PSORIASIS-ASSOCIATED VASCULAR PATHOLOGY

Clinicians have long utilised macroscopically visible, characteristic, vascular abnormalities, the so-called Auspitz (“bloody dew”) phenomenon\[19\] (Figure 1B,C) as an almost pathognomonic diagnostic sign that indicates the presence of psoriasis. This corresponds to prominent, histologically visualised microvascular changes such as vascular dilation and elongation as well as increased blood vessel leakiness and tortuosity.\[20\] Importantly, these vascular changes preceed epidermal hyperplasia in the development of lesions of psoriasis\[21,22\] (Figure 1C). This suggests that the psoriasis-associated microvascular abnormalities play a functionally more important role in the primary pathogenesis of psoriasis than is widely appreciated. Moreover, the clearance of lesions of psoriasis during therapy is accompanied by vascular normalisation.\[23,24\]

The angiogenesis in plaques of psoriasis does not usually include the classical outgrowth of new capillaries from pre-existing vessels, but is characterised by pronounced vascular dilation and elongation as well as enhanced vascular permeability, representing so-called “inflammatory angiogenesis.”\[25,26\] In the skin of healthy individuals, the dermal capillaries show an arterial phenotype whereas the capillary loops in the skin of patients with psoriasis resemble venous capillaries, with a basement membrane (single or multi-layered) and a fenestrated endothelium that contributes to enhanced vascular permeability.\[23\] Treatment of psoriasis restores the arterial phenotype of dermal capillaries evident in the skin of healthy individuals.\[27\]

VEGF-A is highly expressed in the lesional skin of patients with psoriasis compared to non-lesional skin and healthy skin.\[28-30\] In addition, the plasma levels of VEGF-A are higher in patients with psoriasis than in healthy individuals and levels correlate with disease severity.\[31,32\] VEGF-A is mainly produced by activated keratinocytes in the skin of patients with psoriasis.\[29,33\] Smaller amounts of VEGF-A are produced by fibroblasts\[29\] and immune mediators such as mast cells.\[34,35\]

3 | VEGF-A BIOLOGY: SYNOPSIS

VEGF-A is a member of the VEGF superfamily that also includes VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, placental growth factor (PGF) and the endocrine gland-derived vascular endothelial growth factor (EG-VEGF).\[8\] Due to alternative exon splicing, VEGF-A is present in different isoforms with VEGF\(_{121}\) and VEGF\(_{165}\) being the predominant VEGF-A isoforms found in the lesional and non-lesional skin of patients with psoriasis.\[36,37\] VEGF-A binds specifically to VEGFR-1 and VEGFR-2, which are receptor tyrosine kinases (RTKs). VEGFR-1 (also known as Flt-1; fms-like tyrosine kinase) is expressed by several cell types, and VEGFR-2 (also known as KDR/Flik-1; Kinase-insert-Domain-containing Receptor/ Fetal liver kinase-1) is largely endothelial cell specific.

The neuropilins (NRPs), NRP-1 and NRP-2, are a family of non-tyrosine kinase receptors that amplify VEGF-A signalling.\[38\] Other members of the VEGF superfamily, such as VEGF-C and VEGF-D, bind to VEGFR-3 (also known as Flt-4), which is expressed in lymphatic endothelial cells and mediates lymphangiogenesis\[39,40\] (Figure 2).

4 | THE ROLE OF VEGF-A IN ANGIogenesis

Binding of VEGF-A to VEGFR-2 in blood vascular endothelial cells leads to the activation of a network of downstream signalling pathways that mediate angiogenesis\[41\] (Figure 3). While VEGFR-2 is the main mediator of VEGF-A–induced angiogenesis, VEGFR-1 is essential for the recruitment of haematopoietic precursors and migration of monocytes.\[41\] VEGF-A binds to VEGFR-1 with higher affinity than VEGFR-2.\[42\] However, VEGFR-1 has weak kinase activity and binding of VEGF-A on the surface of endothelial cells induces weak phosphorylation.\[43\] Both receptors are important in angiogenesis, and this has been shown in studies where blockade of both VEGFR-1 and VEGFR-2 is needed to abolish VEGF-A–mediated angiogenesis.\[44\] VEGF-A upregulates VEGFR-1 and VEGFR-2 expression in endothelial cells enhancing VEGF-A–mediated functions.

5 | PRECLINICAL EVIDENCE FOR A ROLE OF VEGF-A IN PSORIASIS

A transgenic mouse model that constitutively expresses VEGF-A in the basal keratinocytes under the control of keratin K14 promoter evidences a key role for VEGF-A in the pathogenesis of psoriasis.\[45\] The VEGF-A transgenic mice develop skin lesions resembling human psoriasis at six months of age under basal conditions, suggesting that chronic exposure to high levels of VEGF-A is required for the development of psoriasis-like lesions. These lesions are characterised by epidermal hyperplasia, parakeratosis and mild formation of rete ridge in the ear skin.\[45\] The increased vascularity and inflammatory cell infiltrates in VEGF-A transgenic mouse resemble those in the skin of patients with psoriasis.\[46\]

Moreover, transgenic mice develop prominent rete ridge structures, hyperkeratosis and inflammation in response to injury.\[45\] This pathognomonic phenomenon, termed the Koebner phenomenon,
is one of the characteristic hallmarks of human psoriasis and found only in very few other dermatoses. The psoriasis-like changes are dependent of VEGF-A because VEGF-A blockade reversed the chronic skin inflammation in VEGF-A transgenic mice. In the VEGF-A transgenic mouse, overexpression of VEGF-A by epidermal keratinocytes leads to increased density of tortuous blood capillaries in the dermal papillae and enhanced leukocyte rolling and adhesion in the post-capillary skin venules. The VEGF-A transgenic mice also overexpress VEGFR-1 and VEGFR-2 and have infiltration of mast cells in the upper dermis.

Mice which are heterozygous for the VEGF-A transgene are unable to downregulate experimentally induced inflammation and develop a psoriasis-like phenotype only after being challenged with a sensitising agent in the skin. These mice present elongated rete ridges, hyperplasia, parakeratosis, infiltration of CD8+ T cells in the epidermis and CD4+ T-cell infiltration in the dermis. Moreover, these mice have highly proliferative and enlarged lymphatic vessels, which closely resemble lymphatic vessels in the lesional skin of patients with psoriasis. These findings suggest that abnormal lymphatics may be contributing to the inflammatory response in VEGF-A transgenic mice.

The VEGF-A receptors, VEGFR-1 and VEGFR-2, are expressed on blood endothelial cells. VEGFR-1 is also expressed on epidermal keratinocytes in healthy skin and in the skin of patients with psoriasis. The expression of VEGFR-2 by epidermal keratinocytes is controversial. Although two studies report the expression of VEGFR-2 on epidermal keratinocytes, other large comparative studies of global gene expression in different cell types detected VEGFR-2 expression in endothelial cells but not in non-malignant epithelial cells. Levels of VEGF-A expression in keratinocytes correlate with vascularity in the papillary dermis of plaques of psoriasis. It has been reported that VEGF-A upregulates K6, K16 and K17 expression and downregulates K1 and K10 expression in human epidermal keratinocytes in vitro, suggesting that VEGF-A may play a role as an important regulator of keratin expression in psoriasis.

Deletion of NRP-1 or VEGFR-1 (Flt-1) expression in the epidermis of VEGF-A overexpressing transgenic mice prevents the development of psoriasis-like lesions, suggesting that the development of VEGF-A-induced psoriasis-like lesions is mediated by the interaction between NRP-1 and VEGFR-1 on keratinocytes in VEGF-A transgenic mice. Deletion of VEGFR-1 in the skin of Jun knockout mice, another commonly used mouse model of psoriasis, decreases the severity of psoriasis-like lesions. Taken together, these preclinical in vivo findings in instructive mouse models suggest a key role for keratinocytes in the orchestration of vascular remodelling and infiltration of immune cells in psoriasis.

However, it is now well-recognized that psoriasis develops as the result of a complex crosstalk between keratinocytes and immune cells. Therefore, it is conceivable that VEGF-A drives the development of psoriasis not only through upregulated angiogenesis, but
also directly through the stimulation of epidermal keratinocytes and infiltrating immune cells, such as dendritic cells or macrophages [56] (Figure 4).

### 6 | VEGF-A INHIBITORS IN SKIN INFLAMMATION

In order to understand the complex pathogenesis of psoriasis, a better understanding of the molecular and cellular mechanisms of VEGF-A in the skin of patients with psoriasis is required. Indeed, blockade of VEGF-A with VEGF-Trap (also known as aflibercept; a chimeric immunoglobulin (IgG) Fc or fusion protein that combines immunoglobulin-like domain 2 of VEGFR-1 and domain 3 of VEGFR-2) ameliorated psoriasis-like lesions in VEGF-A overexpressing transgenic mice. [45,57] Systemic administration of VEGF-Trap led to resolution of rete ridge elongations, normalisation of epidermal architecture, reversion of epidermal CD8\(^+\) T-cell infiltrate and normalisation of dermal microvasculature. [45] This suggests that VEGF-A is a key mediator of psoriasis-like inflammation in mice.

Other researchers have attempted to block VEGF-A signalling by targeting its receptors with monoclonal antibodies in mouse models of inflammation. For instance, combined systemic VEGFR-1 and VEGFR-2 blockade with monoclonal antibodies (MF-1; an anti- VEGFR-1 monoclonal antibody and CD101; an anti-VEGFR-2 monoclonal antibody) decreased experimentally induced skin inflammation in mice, including a reduction in skin inflammation, oedema and lymphatic vessel size. [44] Independent administration of either antibody did not have a significant effect on skin inflammation, and single blockade of VEGFR-1 leads to a significant decrease in CD11c\(^+\) macrophages. This study provides evidence that simultaneous blockade of VEGF-A receptors is necessary to improve skin inflammation and demonstrates the importance of both receptors in VEGF-A–mediated functions in the skin. [44] These and other in vivo studies in mice (Table 1) all support the concept that anti-VEGF-A therapies deserve systematic dissection as a novel treatment strategy for psoriasis.

### 7 | VASCULAR LESSONS FROM CURRENT PSORIASIS THERAPY

Biological therapies which target the complex immune signalling pathways involved in the pathogenesis of psoriasis are widely used in psoriasis management. [58,59] In spite of the efficacy of these treatments, their long-term efficacy may be compromised by a variety of factors such as the fact that they hardly prevent relapse and they can lead to serious side effects. [1] Several well-established anti-psoriatic drugs,
such as methotrexate,\textsuperscript{[60]} cyclosporine\textsuperscript{[61]} and retinoids,\textsuperscript{[31]} have anti-angiogenic properties and reduce the levels of VEGF-A in plasma as part of their therapeutic effect (Table 2). In some studies, the down-regulation of VEGF-A as well as the reduction of blood vessel perfusion in plaques of psoriasis correlates with clinical improvement.\textsuperscript{[62,63]}

The gene that encodes for VEGF-A is highly polymorphic, and it is located on chromosome 6p21.3, near PSORS1, the main genetic determinant of psoriasis.\textsuperscript{[27]} Production of VEGF-A is genetically determined and influenced by commonly occurring polymorphisms within the VEGF-A gene. Our group has been at the forefront in describing these single nucleotide polymorphisms (SNPs) and in implicating the two most common polymorphisms in these regions as candidate SNPs in several diseases with a putative angiogenic basis including psoriasis.\textsuperscript{[31,65]}

We have also reported that VEGF-A genotype distinguishes two groups of patients with respect to peripheral blood mononuclear cell (PBMC) production of VEGF-A—"high" and "low" VEGF-A producers.\textsuperscript{[65]} Those with the "high VEGF-A producing" genotype also have significant association with early-onset psoriasis and development of severe disease.\textsuperscript{[31,65]} It has been suggested that those patients with psoriasis who are "high VEGF-A producers" may have an "angiogenic constitution" which predisposes them to develop a severe disease phenotype.\textsuperscript{[28]} This distinct sub-group of
### TABLE 1  Preclinical studies investigating the effect of VEGF-A inhibitors in skin inflammation

| Agent          | Route of administration | Mouse model                                | Type of molecule                      | Main findings in mice                                                                 | Reference |
|----------------|-------------------------|--------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------|-----------|
| VEGF-Trap      | Subcutaneous injection  | Homozygous VEGF-A transgenic mice          | Fusion protein                        | Normalised the epidermal architecture, decreased parakeratosis, decreased vascular hyperplasia and normalised keratin 6, ICAM-1 and E-selectin expression | [45]      |
| MF-1 and CD101 | Intraperitoneal injection | Heterozygous VEGF-A transgenic mice     | Anti-VEGFR-1 and anti-VEGFR-2 mAb | Reduced in skin inflammation, oedema and lymphatic vessel enlargement                  | [44]      |
| NVP-BAW2881    | Oral/topical injection  | Homozygous VEGF-A transgenic mice          | Receptor tyrosine kinase inhibitor     | Decreased cutaneous inflammation, lymphocyte infiltration, hyperkeratosis, lymph node size and blood vessel density | [91]      |
| G6-31          | Subcutaneous injection  | JunB/c-Jun double knockout                 | Anti-VEG-F-A mAb                      | Reduced the number of blood and lymphatic vessels, decreased inflammatory infiltrate and normalised the epidermis | [92]      |
| Valpha         | Subcutaneous injection  | Homozygous VEGF-A transgenic mice          | Chimeric fusion protein. Targets VEGF-A and TNF-α | Reduced epidermal hyperplasia and blood and lymphatic vessel density | [93]      |
| Honokiol       | Topical application     | Homozygous VEGF-A transgenic mice          | Interferes with VEGF-2 phosphorylation and blocks NF-kB activation | Reduced parakeratosis, epidermal thickening and inflammatory infiltration | [94]      |
| Sunitinib      | Topical application     | Imiquimod treated mice                    | Receptor tyrosine kinase inhibitor     | Inhibited keratinocyte proliferation and induced keratinocyte apoptosis                 | [95]      |

### TABLE 2  Psoriasis therapies with anti-angiogenic properties

| Type of treatment | Drug                        | Main mechanism of action                                      | Anti-angiogenic effect                                                                 | Reference |
|-------------------|-----------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------|
| Topical           | Goeckerman therapy (coal tar + UVB) | Inhibits DNA synthesis keratinocytes in the basal layer Anti-proliferative effects | Reduces serum levels of VEGF-A                                                          | [62]      |
|                   | Vitamin D3 analogues (calcipotriol, calcitriol and tacalcitol) | Regulates keratinocyte proliferation/differentiation Anti-proliferative effects | Downregulates EC and keratinocyte proliferation                                        | [96,97]   |
| Light phototherapy | Phototherapy (Psoralen + ultraviolet A, PUVA) | Suppresses keratinocyte proliferation Induces keratinocyte apoptosis Regulates cytokine production | Reduces VEGF-A expression and blood vessel perfusion in plaques of psoriasis Induces EC apoptosis and decreases EC proliferation | [60,94,98,99] |
| Standard systemic therapy | Cyclosporine A | Decreases T-cell activity inhibiting calcineurin Modulates keratinocyte proliferation and differentiation | Inhibits EC migration, downregulates VCAM-1 and ICAM-1 expression Inhibits the release of pro-angiogenic mediators Reduces capillaries diameter | [61,100] |
|                   | Methotrexate               | Reduces keratinocyte and lymphocyte proliferation Induces lymphocyte apoptosis Inhibits T-cell inflammatory action | Reduces VEGF-A expression and blood vessel perfusion in plaques of psoriasis Inhibits EC and T-cell adhesion molecule expression Reduces CD31 expression | [60,101,102] |
| Retinoids (acitretin) | Normalisation of keratinocyte proliferation/differentiation Anti-proliferative effects | Downregulates VEGF-A secretion by keratinocytes. | | [31,65] |
| Biologic therapy  | Anti-TNF-α Infliximab, etanercept and adalimumab | Immunosuppression (blocks TNF-α) | Downregulates EC proliferation Reduces blood vessel diameter and vascular network size | [103,104] |

Abbreviations: EC: endothelial cell; ICAM-1, intercellular adhesion molecule 1; TNF, tumor necrosis factor; UVB, ultraviolet B; VCAM-1, vascular cell adhesion molecule 1.
patients may be those most likely to benefit from an anti-VEGF-A treatment strategy, offering clinicians the opportunity to personalise treatment for psoriasis.

9 | VEGF-A INHIBITION AS A NOVEL STRATEGY FOR THE MANAGEMENT OF PSORIASIS

Anti-angiogenic therapies have become increasingly used in the fields of oncology and ophthalmology. There are different strategies to target the VEGF-A/VEGFR signalling system. These include (a) direct neutralisation of VEGF-A using monoclonal antibodies (e.g. bevacizumab and ranibizumab); (b) inhibition of VEGF-A receptor function using inhibitors of VEGF receptor tyrosine kinase (e.g. sorafenib, regorafenib, sunitinib and vandetanib); and (c) prevention of VEGF-A binding to its receptors (e.g. VEGF-Trap/afiblercept, a decoy receptor fusion protein that captures free VEGF-A) (Figure 5). All these VEGF-A inhibition strategies deserve consideration in the management of psoriasis.

Bevacizumab (Avastin, Genentech) was the first VEGF-A inhibitor to be licensed by the Food and Drug Administration (FDA) in 2004 for the treatment of metastatic colorectal carcinoma and shortly after in 2005 by the European Medicines Agency (EMA). Bevacizumab is a recombinant, humanised, monoclonal antibody (93% human, 7% murine) that binds all isoforms of circulating VEGF-A, preventing VEGF-A binding to its receptors. Bevacizumab is currently licensed for the treatment of metastatic colorectal cancer, non-small-cell lung carcinoma (NSCLC), glioblastoma multiforme of the brain, metastatic renal cell carcinoma, cervical cancer and ovarian cancer. Table 3 summarises the anti-angiogenic and immunomodulatory effects of bevacizumab.

VEGF-A inhibitors are not licensed for the treatment of psoriasis. However, there are two case reports of patients with psoriasis who experienced significant improvement of their disease following treatment with bevacizumab. In one case, a 60-year-old man with a 40-year history of psoriasis and psoriasis affecting 40% of his body surface (PASI score of 16.8) received systemic chemotherapy and bevacizumab and experimented significant clinical improvement (PASI score 1.4) which was maintained during the three-month follow-up.

The second case of bevacizumab-associated improvement in psoriasis was a 65-year-old man with metastatic renal carcinoma, a 40-year history of psoriasis affecting 50% of his body surface area and 30 years of psoriatic arthritis. The patient received bevacizumab and IFN-α, which led to significant clearance of his psoriasis.

FIGURE 5 VEGF-A inhibitors. There are several pharmacological approaches available to inhibit VEGF-A signalling. Bevacizumab is a humanised monoclonal antibody that binds directly to VEGF-A. Ranibizumab is a monoclonal antibody fragment that binds VEGF-A. Sorafenib is a small molecular tyrosine multikinase inhibitor that blocks VEGFR-1 and VEGFR-2 and can inhibit RAF/MEK/ERK pathway. It also targets platelet-derived growth factor beta (PDGFR-β), Flt-3 and c-KIT (not shown). Sunitinib is another multikinase inhibitor that targets VEGFR-1, VEGFR-2 and VEGFR-3. It also targets PDGF alpha and beta (PDGFR-α and PDGFR-β), stem cell factor and Flt-3 (not shown). Regorafenib is a tyrosine multikinase inhibitor that targets VEGFR-1, VEGFR-2 and VEGFR-3. It also targets PDGF-β, fibroblast growth factor receptor (FGFR) 1 and Kit, RET and RAF-1 (not shown). Vandetanib is a tyrosine multikinase inhibitor that targets VEGFR-2. It also targets epidermal growth factor (EGFR) and the proto-oncogene RET (not shown). Afiblercept is a decoy receptor fusion protein that binds VEGF-A, VEGF-B and PGF.
and improvement in arthritis. The bevacizumab treatment was interrupted due to proteinuria and replaced by sorafenib and later with sunitinib, leading to recurrence of psoriasis and arthritis. The sunitinib therapy was discontinued due to raised levels of creatinine and bevacizumab restarted as monotherapy. Three months after bevacizumab re-initiation, there was complete remission of his psoriasis. [78]

A summary of the evidence from case reports of VEGF-A inhibition in psoriasis is beyond the scope of this paper but is presented in Table S1.

Psoriatic arthritis is a systemic disease that causes joint damage, and it is estimated to affect 20 to 30% of patients with psoriasis. [84] Since angiogenesis and VEGF-A also play a key role in the pathogenesis of psoriatic arthritis, patients with this phenotype may profit from a systemic therapy that targets the vasculature. [85,86] A case report of remission of psoriatic arthritis following bevacizumab therapy [78] supports the concept that anti-VEGF-A therapy may be a potential treatment option for both the skin and joint manifestations of psoriasis.

The lymphatic vasculature is key in the initiation and resolution of skin inflammation, although it has been largely overlooked. Lymphatic vessels in plaques of psoriasis are dilated, tortuous and dysfunctional. [87] In mouse models of psoriasis, activation and expansion of the lymphatic vasculature promoted the resolution of inflammation including oedema reduction and downregulation of the inflammatory cell infiltrate. [88] VEGFR-3 and its ligands, VEGF-C and VEGF-D, constitute the main signalling pathway involved in lymphatic development. While angiogenesis enhances skin inflammation, lymphangiogenesis resolves skin inflammation and activation of the lymphatic vasculature could present a novel therapeutic strategy for the management of psoriasis. [87] Therefore, VEGF-A may not be the only plausible target of the VEGF superfamily for psoriasis treatment and VEGF-C and VEGF-D also deserve systematic exploration.

**CONCLUSIONS**

Here, we have delineated a persuasive line of argumentation in support of the hypothesis that vascular dysfunction, namely VEGF-A/VEGFR-driven abnormal angiogenesis in the papillary dermis of lesions of psoriasis, not only is a significant contributor to the overall pathophysiology of psoriasis, but also is a promising target for therapeutic intervention that may exert long-lasting beneficial effects if employed in the future management of psoriasis.
A number of adverse effects are associated with systemic administration of VEGF inhibitors including proteinuria, hypertension and impaired wound healing.[89] Thus, future development of anti-VEGF therapies for the management of psoriasis will require careful evaluation in order to minimise treatment-associated toxicities.

Given the often (but certainly not always) impressive clinical improvement seen with several biologicals routinely employed in current psoriasis management,[58,59,90] we are not advocating that anti-VEGF or VEGF receptor inhibitory therapy should replace these biologicals. Instead, treatment strategies which restore/downgrade the vascular abnormalities in psoriasis may have significant therapeutic utility as adjunctive therapy that accelerates, maximises and prolongs the duration of PASI score improvement achievable with standard psoriasis biologicals. Moreover, specifically targeting anti-angiogenic therapy to those individuals with a prominent "pro-angiogenic" psoriasis phenotype could facilitate personalised therapy regimens and individually tailored adjunctive therapy for a well-defined subpopulation of patients with psoriasis, in particular whenever they show incomplete response to standard therapy.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

HY and RP designed the study, ALM, JHS and HY wrote the viewpoint essay. All authors contributed to the writing/editing of the paper and have read and approved the final version of the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.
Table S1. Case reports of VEGF-A inhibitors in patients with psoriasis.

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