Antivascular endothelial growth factor-A therapy: a novel personalized treatment approach for psoriasis

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Summary

Chronic plaque psoriasis is an inflammatory skin disease in which genetic predisposition along with environmental factors lead to the development of the disease, which affects 2% of the UK’s population and is associated with extracutaneous morbidities and a reduced quality of life. A complex cross-talk between innate and adaptive immunity, the epithelia and the vasculature maintain the inflammatory milieu in psoriasis. Despite the development of promising treatment strategies, mostly targeting the immune system, treatments fail to fulfill every patient’s goals. Vascular endothelial growth factor-A (VEGF-A) mediates angiogenesis and is upregulated in the plaques and plasma of patients with psoriasis. Transgenic expression of VEGF-A in experimental models led to the development of skin lesions that share many psoriasis features. Targeting VEGF-A in vivo models of psoriasis-like inflammation resulted in disease clearance. Anti-angiogenesis treatments are widely used for cancer and eye disease and there are clinical reports of patients treated with VEGF-A inhibitors who have experienced Psoriasis Area and Severity Index improvement. Existing psoriasis treatments downregulate VEGF-A and angiogenesis as part of their therapeutic effect. Pharmacogenetics studies suggest the existence of different genetic signatures within patients with psoriasis that correspond with different treatment responsiveness and disease severity. There is a subset of patients with psoriasis with an increased predisposition to produce high levels of VEGF-A, who may be most likely to benefit from anti-VEGF-A therapy, offering an opportunity to personalize treatment in psoriasis. Anti-VEGF-A therapies may offer an alternative to existing anticytokine strategies or be complementary to standard treatments for the management of psoriasis.

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after an initial satisfactory response. A retrospective study of 250 patients over the course of 9 years reported that biologic therapies fail more often due to secondary failure (24% of failure rate), whereas adverse effects (16% of failure rate) were the main cause of failure for systemic therapies. Unfortunately, even the most efficacious therapies do not achieve skin clearance in all individuals, and this continues to drive the need for the development of new treatments and treatment paradigms. In addition, psoriasis management would also benefit from a personalized management approach where care and treatment are tailored according to the healthcare needs and phenotype of each patient. Matching patients with the right treatments for them could avoid the toxicities associated with treatments, reduce the risk of developing comorbid disease and lead to significant healthcare savings.

Inhibition of angiogenesis has been studied extensively since it was suggested in the 1970s that the growth of new blood vessels was required for tumour growth. Therapeutic strategies for VEGF-A blockade have been developed including: (i) VEGF-A direct neutralization using monoclonal antibodies (mAbs) such as bevacizumab, ranibizumab and ramucirumab; (ii) VEGF-A receptor inhibition using VEGF-A receptor tyrosine kinase inhibitors such as sorafenib, regorafenia, sunitinib and vandetanib; and (iii) prevention of VEGF-A binding to its receptors using a decoy receptor fusion protein that binds to free VEGF-A, such as VEGF Trap (aflibercept). Pharmacological approaches to target the VEGF-A/VEGFR system are now widely used, particularly in the fields of oncology and ophthalmology. However, despite the importance of the vasculature in the pathogenesis of psoriasis, no anti-VEGF-A therapies have been licensed for psoriasis.

In this review, we discuss the potential of targeting the VEGF-A/VEGFR signalling pathway as a promising therapeutic strategy for the management of psoriasis. The scientific data available suggest that anti-VEGF-A therapy is particularly amenable to personalized treatment.

The vasculature in the pathogenesis of psoriasis

Functional and structural abnormalities in the skin vasculature drive the pathogenesis of psoriasis. The appearance of bleeding points upon removal of the superficial scales in psoriasis plaques, the Auspitz sign, is the clinical manifestation of the vascular abnormalities present in the papillary dermis of plaques of psoriasis. VEGF-A and its receptors, VEGFR-1 and VEGFR-2, mediate inflammatory angiogenesis in psoriasis leading to blood vessel dilation and enlargement, enhanced endothelial cell proliferation, vasodilation and vessel hyperpermeability (Figure 2).

The gene that encodes for VEGF-A (VEGFA) is highly polymorphic and is located on the 6p21.3 chromosome near the main genetic loci for psoriasis, PSORS1. VEGF-A polymorphisms have been implicated as candidate single-nucleotide
Figure 2  (a) Chronic plaque psoriasis. Patient with chronic plaque psoriasis with red scaly skin plaques on the upper limbs due to the enhanced vasculature present in the papillary dermis. (b) The role of VEGF-A in the pathogenesis of psoriasis. In plaques of psoriasis, the blood vessels are dilated, enlarged, more tortuous and hyperpermeable. The lymphatic vessels are dilated and nonfunctional. (1) In plaques of psoriasis VEGF-A is mainly produced by keratinocytes, fibroblasts and immune cells such as mast cells. (2) VEGF-A binding to VEGFR-2 on blood vascular endothelial cells leads to the activation of various downstream signalling pathways that contribute to angiogenesis, including endothelial cell proliferation and survival, endothelial cell migration, vasodilation and permeability. As a result, there is an expansion of the blood vascular network in the papillary dermis of plaques of psoriasis. (3) VEGF-A enhances the expression of endothelial cell adhesion molecules including E-selectin, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). This enhances blood vessel permeability and induces leucocyte extravasation from the vessels to the extracellular matrix. (4) Monocytes and macrophages, which express VEGFR-1, exhibit chemotaxis towards VEGF-A. (5) VEGF-A may contribute to the abnormal pattern of keratin expression in plaques of psoriasis. (6) VEGF-A induces the release of pro-angiogenic mediators, i.e. IL-8, tumour necrosis factor (TNF) and IL-17, which contribute to leucocyte recruitment.
polymorphisms (SNPs) for diseases with an angiogenic basis such as diabetic retinopathy and pre-eclampsia. Two of the most common VEGF-A gene SNPs are located in the promoter region at the −460 position and in the 5′-untranslated region at the +405 position of VEGFA, and they determine VEGF-A production. Based on the VEGF-A genotype two groups of patients with psoriasis can be differentiated: 'low VEGF-A producers' and 'high VEGF-A producers'. Patients with the high VEGF-A-producing genotype appear to have an angiogenic constitution that predisposes them to a severe disease phenotype [Psoriasis Area and Severity Index (PASI) score > 12] and early onset (before 40 years of age). Therefore, all patients with psoriasis may benefit from anti-VEGF-A therapies; however, those patients with psoriasis who are 'high VEGF-A producers' may benefit most.

Vascular endothelial growth factor-A in experimental models of skin inflammation

Observations of increased levels of VEGF-A in the skin of patients with psoriasis led to the development of an experimental model to study the effects of VEGF-A in the skin. Homozygous transgenic (TG) overexpression of VEGF-A in epidermal keratinocytes using the keratin 14 promoter in mice – VEGF-A TG mice – led to the spontaneous development of skin lesions sharing the key histological, immunological and clinical features of psoriasis (including the Koebner phenomenon). Histologically, the psoriasis lesions demonstrate rete ridge formation, hyperplasia and parakeratosis in the epidermis together with blood vessel elongation, dilation and increased tortuosity in the papillary dermis; and inflammatory cell infiltration in the dermis. The VEGF-A TG mice also have increased VEGF-A receptor expression, enhanced leucocyte rolling and adhesion in the postcapillary venules and infiltration of mast cells in the upper dermis.

In subsequent studies, researchers observed that heterozygous VEGF-A TG mice develop their psoriasis-like phenotype after being challenged with a skin-sensitizing agent rather than spontaneously like homozygous VEGF-A TG mice. Heterozygous VEGF-A TG mice develop chronic skin inflammation in response to experimentally induced skin hypersensitivity and present the key histological hallmarks of psoriasis including rete ridge elongation, hyperplasia, parakeratosis, increased vascular permeability, epidermal CD8+ T-cell infiltration and dermal CD4+ T-cell infiltration. Heterozygous VEGF-A TG mice are unable to downregulate inflammation, allowing researchers to experimentally induce chronic inflammation under controlled conditions.

The lymphatic vessels are essential in immune surveillance in the skin as they transport immune cells and inflammatory mediators between the lymph nodes and the skin. In inflammatory situations such as psoriasis, their function is to clear extravasated fluid originated from leaky inflamed blood vessels and to maintain tissue fluid homeostasis. However, lymphatics in psoriasis are dilated, tortuous and dysfunctional, impeding their normal function and promoting inflammation. Members of the VEGF family, VEGF-C and VEGF-D, mediate lymphangiogenesis in the skin through VEGFR-3, expressed on lymphatic endothelial cells. Studies in VEGF-A TG mice also permitted understanding of the hitherto unknown contribution of the lymphatic vessels to psoriasis pathogenesis, which are enlarged and proliferating in chronically inflamed skin. Indeed, VEGF-A-mediated lymphatic dysfunction contributes to maintenance of chronic skin inflammation in heterozygous VEGF-A TG mice. Restoration of lymphatic function in heterozygous VEGF-A TG mice via simultaneous targeting of VEGFR-1 and VEGFR-2 led to resolution of inflammation, reduced oedema, decreased epidermal thickening, inflammatory infiltrate and increased drainage. Restoration of the lymphatic vessels in experimental models of other immune-mediated inflammatory diseases including inflammatory bowel disease, rheumatoid arthritis and skin inflammation, results in reduced oedema and resolution of inflammation. Anti-VEGF-A therapy offers the opportunity to simultaneously target angiogenesis and lymphatic dysfunction, removing the potential to develop new lesions and speeding the resolution of existing ones.

Vascular endothelial growth factor-A inhibition in experimental models of psoriasis

Targeting the VEGF-A/VEGFR system has been investigated in mouse models of psoriasis-like inflammation. Different strategies including directly targeting VEGF-A using mAbs and fusion proteins, as well as targeting VEGF-A receptors using tyrosine kinase inhibitors, have successfully downregulated psoriasis-like inflammation in mice. Treating the VEGF-A TG mice with a high-affinity soluble decoy receptor that targets VEGF-A (VEGF Trap: aflibercept), ameliorated the psoriasis-like skin changes including decrease in parakeratosis and in vascular hyperplasia; downregulated keratin 6 expression, a marker of keratinocyte abnormal differentiation; reverted epidermal CD8+ T-cell expression and downregulated E-selectin, a marker of vascular inflammation. In further investigations, VEGF-A and TNF-α were simultaneously targeted in the VEGF-A TG mice using a chimeric fusion protein (Valpha), resulting in reduced epidermal hyperplasia, decreased inflammation and reduced blood and lymphatic vessel density.

Simultaneous VEGFR-1 and VEGFR-2 receptor blockade with two mAbs (MF-1 and CD101 block VEGFR-1 and VEGFR-2, respectively) led to a reduction in skin inflammation, oedema and lymphatic vessel size in mouse models of inflammation. Independent administration of either antibody did not have a significant effect on skin inflammation, suggesting that both VEGF-A receptors participate in maintaining skin inflammation. VEGF-A blockade with a mAb (G6-31) in the JunB/c-Jun double knockout mouse model of psoriasis-like inflammation led to a decrease in the size of blood and lymphatic vessels, reduced number of blood vessels and downregulation of macrophage, lymphocyte and neutrophil infiltration.

The tyrosine kinase domain of VEGFR-2 was inhibited in the VEGF-A TG mice, leading to reduced cutaneous inflammation, decreased lymphocyte infiltrate and decreased lymph
node tyrosine kinase inhibitor, termed NVP-BAW2881, also decreased blood vessel expansion and reduced epidermal hyperproliferation and hyperkeratosis. NVP-BAW2881, which can be orally and topically administered, exhibited similar effects on mice skin independent of the administration route. However, the topical form was reported to be safer and more efficient as it overcame some of the orally associated side-effects such as gastrointestinal perforation.59 Sunitinib, a multitargeted tyrosine kinase inhibitor was able to alleviate psoriasis-like inflammation in the imiquimod-induced mouse, a widely used model of psoriasis-like inflammation, by regulating keratinocyte proliferation and apoptosis.60 Honokiol, a natural product isolated from magnolia plant species, which interferes with VEGFR-2 phosphorylation and has anti-angiogenic properties, had an anti-inflammatory effect in the VEGF-A TG mice by reducing parakeratosis, epidermal thickening and inflammatory infiltrate.61 These preclinical studies underscore the importance of targeting VEGF-A in the management of psoriasis.

Anti-angiogenic therapy in psoriasis

Although anti-angiogenic therapy is not licensed for psoriasis, some of the conventional treatments for psoriasis have significant anti-angiogenic properties and decrease the levels of VEGF-A in skin and plasma (Table 1).62 This mechanism of action, which is often unrecognized, undoubtedly contributes to their efficacy and deserves further investigation.

In addition, there are seven case reports of patients who had improvement of psoriasis after being treated for other conditions with anti-angiogenic drugs that specifically target the VEGF-A/VEGFR pathway. Two patients experienced psoriasis improvement after treatment with bevacizumab (Avastin), a mAb to VEGF-A.63,64 The first patient, a 60-year-old male with a 40-year history of psoriasis covering 40% of his body surface, received bevacizumab treatment for metastatic colon cancer and experienced significant improvement in psoriasis (PASI reduced from 16.8 to 1.4).63 This improvement was maintained during the 3-month follow-up.63 The second patient, a 65-year-old male with a 40-year history of psoriasis affecting 50% of his body surface area and 30-year history of PsA, received bevacizumab and interferon (IFN)-α for metastatic renal carcinoma.64 This patient experienced significant improvement in psoriasis (<1% body surface area) and PsA. Interruption of treatment with bevacizumab treatment and replacement with sorafenib and later by sunitinib, due to proteinuria, led to recurrence of psoriasis and PsA.64

There are two cases of improvement in psoriasis associated with sunitinib (Sutent®, a VEGF-A receptor tyrosine kinase inhibitor).65 The first patient, a male with a 20-year history of psoriasis, received IFN-γ during randomized clinical trials for the comparison of IFN-γ and sunitinib efficacy. IFN-γ was discontinued after 6 months due to an increase in psoriasis severity and sunitinib commenced, leading to clearance of psoriasis.65 The second case reported was a 60-year-old patient with a 5-year history of psoriasis who experienced significant improvement in psoriasis within 2 weeks of starting treatment with sunitinib.66

Three cases of patients who experienced significant psoriasis improvement after sorafenib (Nexavar®, a VEGF-A receptor tyrosine kinase inhibitor) treatment have also been reported. A 78-year-old male with a 56-year history of psoriasis experienced psoriasis improvement after 3 weeks of sorafenib treatment for metastatic renal cell carcinoma.62 In another case report, a 71-year-old male with psoriasis was treated with sorafenib for chronic hepatitis C virus infection, achieving complete remission of his psoriatic lesions after sorafenib administration.68 The third case report was a 65-year-old male with hepatocellular carcinoma and 10% of the body area covered by psoriasis plaques, who experienced almost complete remission of psoriasis after receiving sorafenib treatment for 3 months.69

A single-centre, randomized, open-label, dose-comparison clinical trial was performed on patients with psoriasis with a molecule obtained from shark cartilage, termed AE-941, with multiple anti-angiogenic mechanisms.70 The anti-angiogenic mechanisms of AE-941 have been shown in in vitro and ex vivo experiments and include inhibition of matrix metalloproteinase (MMP)-2, MMP-9 and MMP-12, which facilitate vascular remodelling and sprouting through degradation of proteins within the extracellular matrix;71 interference with VEGF-A signalling by competing with VEGF-A binding to its receptor in endothelial cells and inhibition of VEGF-A-mediated VEGFR-2 phosphorylation; inhibition of VEGF-A-mediated microvessel sprouting;72 and increase in the levels of IL-10 (anti-angiogenic cytokine).73 Forty-nine patients were enrolled in the study and 33 completed the 12-week treatment. Patients were randomly allocated to receive one of the four different doses of AE-941, which was administered orally twice a day. AE-941 induced PASI improvement in a dose-dependent way and up to 50% PASI reduction was achieved by patients receiving the highest doses.70

Hypothesizing that the constitutive vascular abnormalities present in psoriatic skin could be ameliorated with VEGF-A blockade, we developed an ex vivo model to investigate the effects of VEGF-A blockade in healthy human skin using a mAb for VEGF-A (bevacizumab, Avastin®).74 Healthy skin was collected from donors and incubated with bevacizumab at clinically relevant doses in the laboratory. Bevacizumab blocked all free VEGF-A and induced endothelial cell apoptosis in healthy human skin ex vivo.74 Subsequently, we adapted our healthy skin organ culture model to study VEGF-A blockade in psoriatic skin ex vivo, observing a reduction in the expansion of blood vessels in skin samples collected from plaques of psoriasis treated with bevacizumab compared with control in a pilot study (unpublished evidence). Using our working and validated ex vivo psoriatic skin organ culture model, we plan to define the molecular signalling pathways that underlie psoriasis improvement induced by anti-VEGF-A therapy. Our studies will impact significantly on the scientific understanding of vascular pathophysiology in psoriasis and provide proof-of-principle for the development of a novel anti-VEGF-A treatment strategy, enhancing the opportunity to offer personalized therapeutics for psoriasis management in the future.
Personalized approaches to psoriasis

Personalized management is an emerging approach that involves tailoring care and treatment according to individual patients’ needs and wishes. Personalized care comprises a patient-centred approach that focuses care on the needs, preferences and values of the individual, ensuring that these factors guide shared clinical decision making. Personalized medicine matches individuals with the best treatment for them, while considering their unique genetic background and disease phenotype. Thus, patients receive treatments with predictable efficacy, reducing their exposure to side-effects of nonefficacious alternatives.

Table 1 Psoriasis treatments with anti-angiogenic properties

| Drug (FDA approval year for psoriasis) | Anti-angiogenic mechanism | Main mechanism of action | Chemical classification | Ref. |
|---------------------------------------|----------------------------|--------------------------|-------------------------|------|
| Topical therapy                       |                            |                          |                         |      |
| Goeckermann therapy (coal tar + UVB)  | Reduction of serum levels of VEGF-A | DNA synthesis inhibition in basal keratinocytes and antiproliferative effects | Coal tar is a mixture of phenols, polycyclic aromatic hydrocarbons and heterocyclic compounds | 91   |
| Calcipotriol, calcitriol and tacalcitol | Inhibition of EC and keratinocyte proliferation | Reduction of keratinocyte proliferation, T-cell and DC modulation | Vitamin D3 analogues | 92,93 |
| Phototherapy (psoralen + UVA)         | Reduction of VEGF-A serum levels | Inhibition of keratinocyte proliferation and induction of keratinocyte apoptosis; regulation of cytokine production | Psoralen belongs to the family of organic compounds known as furanocoumarins | 61,94–96 |
| Standard systemic therapy             |                            |                          |                         |      |
| Methotrexate (1972)                   | Reduction of VEGF-A mRNA, decrease in capillary perfusion, downregulation of EC proliferation, inhibition of EC adhesion molecule expression (ICAM-1, VCAM-1, E-selectin) and decrease in leucocyte infiltration in the skin | Antiproliferative action mediated via the inhibition of dihydrofolate reductase; inhibits purine, methionine and thymidylate synthesis; regulates gene expression in T cells | Folate analogue metabolic inhibitor with antineoplastic properties | 96–98 |
| Acitretin (1996)                      | Downregulation of VEGF-A secretion by keratinocytes | Binds to retinoic acid receptors regulating gene expression; induces keratinocyte differentiation and decreases keratinocyte proliferation | Retinoid and vitamin A derivative | 20,83 |
| Ciclosporin A (1997)                  | EC migration inhibition, reduction in blood vessel diameter, inhibition of the expression of EC adhesion molecules (ICAM and VCAM), inhibits the synthesis of pro-angiogenic factors and stimulates release of anti-angiogenic factors | Calcinium inhibitor that leads to impairment of transcription of IL-2, IFN-γ and TNF-α; T-cell activation suppression | Cyclic nonribosomal peptide of 11 amino acids | 99,100 |
| Biologic therapy                     |                            |                          |                         |      |
| Etanercept (2004)                     | Reduction of VEGF-A and regression of the number of enlarged capillaries | TNF-α inhibitor | Dimeric human fusion protein that mimics TNF-α receptor | 101   |
| Infliximab (2006)                     | Reduction of VEGF-A, Ang 2 and Tie2; downregulation of EC measured as reduction in CD31 expression | TNF-α inhibitor | Chimeric IgG1κ mAb that binds to soluble and transmembrane forms of TNF-α | 102   |
| Adalimumab (2008)                     | Reduction of endothelial cell proliferation, vascular network size and vessel diameter | TNF-α inhibitor | Human mAb against TNF-α | 103   |

DC, dendritic cell; EC, endothelial cell; FDA, US Food and Drug Administration; ICAM, intercellular adhesion molecule; IFN, interferon; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; mRNA, messenger RNA; TNF, tumour necrosis factor; UV, ultraviolet; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

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Genetic and biological markers could be used to predict responsiveness to biologic treatment in psoriasis. For instance, the HLA-C*06:02 genotype, the main genetic susceptibility determinant for psoriasis, is a predictive biomarker of biologic treatment response for two of the most common biologic treatments used for psoriasis: adalimumab (Humira®, a TNF-α inhibitor) and ustekinumab (Stelara®, which inhibits IL-17 signalling by targeting the p40 subunit present in IL-12 and IL-23). HLA-C*06:02-positive patients are more likely to respond to treatment with ustekinumab than HLA-C*06:02-negative patients, who are more likely to respond to adalimumab. The clinical utility of therapeutic drug monitoring in psoriasis was assessed in a multicentre prospective observational cohort of 544 patients with psoriasis receiving adalimumab and in a prospective observational cohort of 491 adults treated with ustekinumab. These studies demonstrated that serum drug levels of adalimumab and ustekinumab could predict treatment response in psoriasis and may have utility in guiding dosing schedules and optimized treatment outcomes.

Personalized medicine based on VEGF-A genetic signatures may offer a means to predict treatment response to anti-VEGF-A therapy. Genetic factors influence the response to anti-VEGF-A therapy in age-related macular degeneration for which novel SNPs have been identified to be associated with lack of treatment response. Two VEGF-A SNPs, +405 and –460, are close to the functional activator protein-1 sites, through which retinoids can block production of VEGF-A. The interaction between genetic control of VEGF-A production and response to acitretin treatment (a retinoid) was investigated in patients with psoriasis and a relation between the –460 genotype and prediction of response to treatment was found. Retinoic acid inhibits VEGF-A production by keratinocytes in a genotype-dependent way but stimulates VEGF-A production by peripheral blood mononuclear cells independent of genotype. These findings suggest that the VEGF-A genotype may predict response to acitretin treatment in patients with psoriasis.

Anti-VEGF-A therapy may be a useful therapeutic option for the clinical subset of patients with psoriasis who have a genetic predisposition to develop a severe phenotype and produce high levels of VEGF-A. Patients who fail to respond to conventional therapy could be identified before starting biologic treatment on the basis of their individual angiogenic proteomic/genomic signatures. Targeting the VEGF-A pathway may offer an alternative to the usual anticytokine strategies or could complement them to help achieve optimal patient outcomes.

**Conclusion**

VEGF-A, which is overexpressed in psoriasis, mediates blood and lymphatic vascular abnormalities in psoriasis, playing a key role in its pathogenesis. VEGF-A-mediated angiogenesis contributes to the development of plaques of psoriasis, and lymphatic vessel dysfunction prevents the resolution of inflammation in psoriasis. The VEGF-A genotype determines VEGF-A production and two groups of patients with psoriasis can be differentiated based on their VEGF-A signature: high and low VEGF-A producers. VEGF-A SNPs are associated with psoriasis and with the severe psoriasis phenotype. The evidence suggests that targeting VEGF-A/VEGFR is a promising treatment strategy for patients with psoriasis. In addition, patients with psoriasis who have a severe phenotype and those who have a genetically determined ‘pro-angiogenic constitution’ may benefit most from anti-VEGF-A therapy, offering dermatologists an opportunity to tailor treatment and offer a personalized approach to management.

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