VEGF as an activity marker in rheumatoid arthritis

Evaluation of: Ozgonenel L, Cetin E, Tutun S, Tonbaklar P, Aral H, Guvenen G: The relation of serum vascular endothelial growth factor level with disease duration and activity in patients with rheumatoid arthritis. *Clin. Rheumatol.* 29(5), 473–477 (2010). VEGF is a crucial mediator of angiogenesis. It has been implicated in neovascularization associated with cancer metastasis, as well as arthritis. Hypoxia present in the inflamed joints, as well as hypoxia-inducible factors mediate VEGF production that leads to endothelial cell prolifertaion and angiogenesis. Serum VEGF levels have been associated with the clinical activity of rheumatoid arthritis. VEGF targeting using anti-VEGF and anti-VEGF receptor antibodies, small molecule inhibitors of VEGF signalling has been utilized in oncology and, very recently, in arthritis therapy.

KEYWORDS: angiogenesis ■ rheumatoid arthritis ■ vascular endothelial growth factor

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VEGF has been implicated in inflammatory mechanisms, as well as in angiogenesis underlying rheumatoid arthritis (RA) [1–3]. VEGF is primarily produced by synovial fibroblasts in the pannus [4]. Proinflammatory cytokines such as TNF-α and IL-1, stimulate synovial fibroblasts and other cells to release VEGF [1,5]. VEGF induces endothelial cell proliferation and migration in *in vitro* culture systems and it also stimulates capillary formation in *in vivo* models of angiogenesis [1,5]. Abundant production of VEGF has been described in RA [1,4,6,7]. In addition, increased serum VEGF levels were correlated with disease activity in RA [4,8,9], ankylosing spondylitis and psoriatic arthritis [10,11].

In the evaluated paper [12], Ozgonenel *et al.* assessed serum VEGF levels in RA patients and correlated VEGF production with disease activity and various phases of the disease. Altogether, 40 RA patients and 38 healthy control subjects were included in the study. Authors classified RA patients into four subgroups with regards to disease activity indicated by DAS28. Thus, RA patients exerted high (DAS28 > 5.1; n = 14), moderate (DAS28 3.2–5.1; n = 22), low disease activity (DAS28 2.6–3.2; n = 3) or remission (DAS28 < 2.6; n = 1). Furthermore, 15 patients had early (disease duration < 2 years) and 25 had late (disease duration ≥ 2 years) disease.

VEGF production was significantly increased in RA patients in comparison with healthy controls. Patients with longer disease duration exerted significantly higher serum VEGF levels in comparison with patients with early RA. Patients in remission and those with low disease activity were dropped during the analysis due to the low patient numbers. RA patients with moderate disease activity had VEGF production comparable to healthy controls. Only RA patients with high disease activity exerted significantly higher serum VEGF levels in comparison with either patients with moderate disease activity or healthy subjects. Serum VEGF levels could be correlated with systemic inflammation indicated by erythrocyte sedimentation rate (ESR) but not with rheumatoid factor.

This study supports reports by other authors indicating that VEGF may serve as an activity marker in RA. Furthermore, increased VEGF production was associated with longer disease duration. Previous studies attempting to correlate VEGF production with disease duration have given conflicting results [13,14].

In this study, serum VEGF was not only associated with high disease activity indicated by DAS28, but also with ESR. High-grade systemic inflammation observed in active RA has indeed been associated with the perpetuation of synovial angiogenesis including VEGF-mediated neovascularization [1,15,16]. Increased hypoxia has been associated with active RA synovitis [17,18] and hypoxia indirectly induces VEGF production and VEGF-mediated angiogenesis via the hypoxia-inducible factor (HIF) pathway [15,17–20]. Hypoxia, HIF and VEGF has been associated with angiogenic, as well as inflammatory events underlying RA [15,17,19].

future medicine part of fsg

Certainly, the targeting of VEGF is a feasible anti-inflammatory and antiangiogenic therapeutic strategy in arthritides, as well as in malignancies [15,21–23]. VEGF or VEGF receptor (VEGFR) inhibition may include the use of monoclonal antibodies to VEGF or VEGFR, soluble VEGFR constructs, small molecule VEGF and VEGFR inhibitors or inhibitors of VEGF and VEGFR signaling [5,21,23–25]. Apart from malignancies, VEGF or VEGFR inhibition has been recently introduced to arthritis trials [21,24,26,27]. Additional studies are required in order to determine the role of VEGF in early versus late arthitis, as well as its involvement in joint destruction.

Future perspective

The hypoxia–HIF–VEGF–angiopoietin system has been targeted in oncology. Antibodies, such as bevacizumab, as well as several small molecule VEGFR tyrosine kinase inhibitors including vatalanib, sunitinib malate, sorafenib, vandetanib, cediranib, masitinib, axatinib and others have been developed and introduced to cancer therapy. Some of these agents, such as vatalanib, have already been tried in animal models of arthritis. There have also been recent attempts to target HIF-1 signaling in inflammatory bowel disease and recently in arthritis. Thus, more and more VEGF and HIF inhibitors may be introduced to the therapy of arthritis in the future.

Financial & competing interests disclosure

Alisa E Koch receives research support from NIH R01 grant #AR048267. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Synovial angiogenesis leads to the perpetuation of rheumatoid arthritis.
- VEGF is the major mediator of synovial angiogenesis.
- VEGF production has been correlated with clinical activity in arthritis.
- VEGF and VEGF receptor targeting may be introduced in the therapy of arthritis, as well as malignancies.

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