Serum Vascular Endothelial Growth Factor Levels Lack Predictive Value in Patients with Active Ankylosing Spondylitis Treated with Golimumab

Jürgen Braun, Xenofon Baraliakos, Kay-Geert A. Hermann, Stephen Xu, and Benjamin Hsu

ABSTRACT. ***Objective.*** To assess vascular endothelial growth factor (VEGF) correlations with new bone formation and bone marrow edema in patients with ankylosing spondylitis (AS) treated with golimumab (GOL).
Methods. Following placebo control (through weeks 16 and 24), GO-RAISE (A Multicenter Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF-α Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis; ClinicalTrials.gov: NCT00265083) all patients received GOL; sera/images were available at weeks 0, 104, and 208. Lateral spinal radiographs and magnetic resonance imaging (MRI) were scored using the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) and the Ankylosing Spondylitis Spinal MRI activity score, respectively.
Results. VEGF levels and the mSASSS did not significantly correlate. Logistic regression analyses showed no association between VEGF levels and an increased risk of syndesmophyte formation at weeks 104 and 208. Pretreatment/Week 14 VEGF did not predict MRI scores/changes at Week 104.
Conclusion. Serum VEGF did not predict radiographic progression/spinal inflammation in patients receiving antitumor necrosis factor. (First Release March 1 2016; J Rheumatol 2016;43:901–6; doi:10.3899/jrheum.150897)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS TUMOR NECROSIS FACTOR
BIOLOGIC BIOMARKERS RADIOGRAPH

Ankylosing spondylitis (AS) is a chronic rheumatic disease of the axial skeleton, initially characterized by spinal inflammation and typically followed by new bone formation evident as syndesmophytes and ankylosis. Biologic agents inhibiting cytokines in the AS inflammatory cascade, including tumor necrosis factor (TNF), can significantly reduce AS signs/symptoms[1] and also have significantly reduced magnetic resonance imaging (MRI)-detected spinal inflammation[2,3]. In the phase III, randomized, placebo-controlled, GO-RAISE trial (A Multicenter Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF-α Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis) of golimumab (GOL) in AS, improvements in spinal inflammation were sustained through treatment Week 104 and correlated with improved disease activity and acute-phase reactants[2]. The ability of anti-TNF intervention to reduce spinal radiographic progression is less clear[4,5,6,7,8]. A biomarker measured prior to/early in anti-TNF therapy that can reliably predict longterm response or reduced radiographic progression would be valuable.

Vascular endothelial growth factor (VEGF) is a signal protein produced by vasculogenesis/angiogenesis-stimulating cells. In rheumatoid arthritis, VEGF is released in response to TNF[9]. VEGF and transforming growth factor-β may be involved in psoriasis[10].

Serum VEGF levels are known to decrease in anti-TNF–treated patients with AS demonstrating clinical improvement[11,12], and an observational study in spondyloarthritis suggested that VEGF level predicted radiographic progression[13]. We reported on the relationships between serum VEGF levels, radiographic progression, and MRI-detected spinal inflammation using longitudinal data from GO-RAISE (GOL in active AS).

MATERIALS AND METHODS

Study design/patients. The phase III, multicenter, randomized,

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placebo-controlled, double-blind, GO-RAISE trial (ClinicalTrials.gov: NCT00265083) was approved by each site's ethical body. All patients provided written informed consent. The GO-RAISE patient selection criteria and study design have been described elsewhere[14,15]. Patients had definite AS according to the modified New York criteria[16], and active disease defined as a Bath Ankylosing Spondylitis Disease Activity Index[17] score ≥ 4 and a total back pain visual analog scale score ≥ 4.

Patients with active AS were randomly assigned (1:1.8:1.8) to receive subcutaneous doses of placebo, GOL 50 mg, or GOL 100 mg at baseline and every 4 weeks (q4week). Randomization was stratified by investigational study site and screening C-reactive protein level (≤ 1.5 mg/dl, > 1.5 mg/dl). Placebo-randomized patients with < 20% improvement in total back pain and morning stiffness entered double-blind early escape at Week 16; the study was placebo-controlled from weeks 0–16. At Week 24, all patients still receiving placebo crossed over to receive GOL 50 mg. All patients continued double-blind treatment through Week 100.

The GO-RAISE longterm extension started with the Week 104 open-label GOL administration. At the investigator's discretion, the GOL dose could be increased from 50 mg to 100 mg q4week or decreased from 100 mg to 50 mg q4week during the longterm extension[18].

Biomarker assessments. Serum samples collected at weeks 0, 4, 14, 24, and 104 of the GO-RAISE trial were tested for selected markers using an ELISA platform by Quintiles Laboratories[19].

Imaging assessments. Lateral view radiographs of the cervical and lumbar spine were performed at weeks 0, 104, and 208. Radiographs were scored using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) method (range 0–72)[20], whereby scores of 0, 1, 2, and 3 indicated normal vertebral unit (VU); VU with erosion, sclerosis, or squaring; VU with syndesmophyte; and VU with bridging syndesmophyte, respectively. Serial spine MRI scans of the cervical, thoracic, and lumbar spine in the sagittal plane were acquired at weeks 0, 14, and 104 with the patient in the supine position using 1.5 Tesla scanners and phase array spine or quadrature coils. Image sequences were scored using the Ankylosing Spondylitis spine MRI-activity (ASspiMRI-a) score (range 0–138)[2,21]. Radiographs and MRI scans were read by 2 qualified, experienced, and independent readers who were blinded to treatment information, patient identity, and chronology of the images, as described previously[2,8].

Syndesmophyte formation was defined as having ≥ 1 vertebral level on radiograph that changed from a score < 2 at baseline to 2 or 3 at Week 104 or 208 according to ≥ 1 reader. Radiographic progression was defined as ≥ 2-unit change in the mSASSS from baseline to Week 104 or 208.

Statistical analysis. Analyses of imaging data collected through Week 208 used only observed data. ANOVA using van der Waerden ranking methodology assessed differences in VEGF levels at Week 0 and changes at weeks 14 and 24 between patients with mSASSS change ≥ 2 versus < 2 at weeks 104 and 208. The relationships between VEGF levels and the ASspiMRI-a scores were assessed by Spearman correlation coefficients (r_s). P values were adjusted for testing multiplicity using the Bonferroni methodology.

Logistic regression analyses were conducted to assess whether VEGF levels conferred an increased risk of syndesmophyte formation or radiographic progression at Week 104 or 208 after treatment adjustment. Receiver-operating characteristic (ROC) curve analyses assessed whether VEGF levels were able to predict subsequent syndesmophyte formation or radiographic progression.

RESULTS

Analysis groups. One hundred forty patients had sera collected for biomarker evaluations, including VEGF; 98 patients at 10 sites with MRI capability participated in the GO-RAISE MRI substudy[2]. Most randomized patients (299/356, 84.0%) had pre- and posttreatment spine radiographs scored by the mSASSS. Patients with data available for Spearman correlation analysis included 85–109 patients with VEGF and the mSASSS data and 33–69 patients with VEGF and the ASspiMRI-a data, both across the various timepoints assessed. In total, 134 patients had both syndesmophyte and VEGF data at ≥ 1 timepoint.

About 20%–25% of the patients in each group were initially assigned to placebo. Baseline characteristics for patients with mSASSS and VEGF data through Week 104 were generally consistent with those of the overall GO-RAISE patient population[2], but showed differences in baseline disease activity between those who progressed and those who did not progress (Appendix 1).

Serum VEGF levels. Spearman correlations indicated no significant association between VEGF and the mSASSS. ROC analysis confirmed there was no association between baseline VEGF and baseline syndesmophytes (data not shown). No significant differences were observed in mean baseline or changes in VEGF levels between patients with change from baseline in mSASSS scores < 2 (those who did not progress) versus ≥ 2 (those who progressed) at Week 104 or 208, or between patients with ≥ 1 new versus no new syndesmophytes at Week 104 or 208 (Table 1). Logistic regression showed no increased risk of syndesmophyte formation or radiographic progression at Week 104 or 208 to be associated with VEGF levels/changes, and ROC analysis showed that using VEGF at baseline, Week 14, or Week 24 to predict syndesmophyte formation or mSASSS progression at Week 104 or 208 was no different from random chance (data not shown).

While a good correlation score was observed between changes in the ASspiMRI-a levels and VEGF levels at Week 14 ($p = 0.001$), other correlational findings indicated that baseline and Week 14 VEGF levels predicted neither future ASspiMRI-a scores nor MRI change scores at Week 104 (Table 2). Figure 1 provides an overview of the VEGF, mSASSS, and ASspiMRI-a findings, demonstrating the initial VEGF decline followed closely by decreased spinal inflammation, with both variables being largely uncoupled from radiographic findings through Week 208.

DISCUSSION

Previous findings have shown that VEGF levels decrease several weeks after anti-TNF therapy initiation[11]. Our analysis extends these findings by showing that VEGF levels do not predict radiographic progression in patients treated with anti-TNF, although we could confirm that VEGF reduction and MRI-detected spinal inflammation correlate. These findings are consistent with the well-documented ability of TNF antagonists to potently reduce serum inflammatory markers and spinal inflammation acutely, but not to halt radiographic progression in the first years of treatment[4,5,6], and also with findings from sequential images obtained through MRI and radiograph in the European Ankylosing Spondylitis Infliximab Cohort (EASIC) study[22].

In the GO-RAISE cohort, Spearman correlation analyses

Table 1. Serum VEGF levels (pg/ml) through Week 24 and subsequent radiographic progression or syndesmophyte formation.

Timepoint	mSASSS Change ≥ 2	mSASSS Change < 2	p*
Week 104			
Baseline, n	23	86	
Median	103.3	77.2	0.2169
Mean ± SD	113.4 ± 71.39	91.7 ± 60.26	
Change from baseline to Week 14, n	23	78	
Median	–19.3	–15.0	0.5968
Mean ± SD	–25.7 ± 36.26	–20.9 ± 29.64	
Change from baseline to Week 24, n	23	77	
Median	–16.1	–16.5	0.6793
Mean ± SD	–23.6 ± 43.65	–18.0 ± 23.25	
Week 208			
Baseline, n	26	67	
Median	68.3	83.9	0.3867
Mean ± SD	95.3 ± 65.78	102.9 ± 65.69	
Change from baseline to Week 14, n	25	61	
Median	–11.4	–22.7	0.2568
Mean ± SD	–17.8 ± 33.53	–24.2 ± 32.81	
Change from baseline to Week 24, n	25	60	
Median	–16.1	–17.5	0.7990
Mean ± SD	–21.6 ± 34.25	–20.0 ± 28.71	
Timepoint	**≥ 1 New Syndesmophyte**	**No New Syndesmophytes**	**p****
Week 104			
Baseline, n	40	94	
Median	86.6	79.9	0.2937
Mean ± SD	109.7 ± 73.66	95.7 ± 66.40	
Change from baseline to Week 14, n	38	86	
Median	–15.9	–16.0	0.8628
Mean ± SD	–20.2 ± 35.83	–22.0 ± 35.82	
Change from baseline to Week 24, n	38	85	
Median	–21.5	–15.9	0.2635
Mean ± SD	–25.0 ± 34.75	–16.7 ± 26.60	
Week 208			
Baseline, n	49	85	
Median	72.4	83.9	0.8931
Mean ± SD	102.7 ± 74.94	98.3 ± 65.19	
Change from baseline to Week 14, n	47	77	
Median	–13.1	–17.3	0.4734
Mean ± SD	–20.0 ± 37.87	–22.3 ± 34.51	
Change from baseline to Week 24, n	47	76	
Median	–16.1	–16.2	0.5956
Mean ± SD	–18.2 ± 35.21	–19.9 ± 25.51	

* P value for comparison of patients with mSASSS change ≥ 2 vs < 2. ** P value for comparison of patients with ≥ 1 vs 0 new syndesmophytes. VEGF: vascular endothelial growth factor; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score.

and logistic regression showed no significant association between VEGF levels/changes with subsequent structural changes/spinal inflammation measured by mSASSS/ASspiMRI-a scores, respectively. The lack of corroboration with findings of Poddubnyy, *et al*[13], suggesting that VEGF is predictive of radiographic progression, is most likely explained by the major difference in treatment. In the GO-RAISE trial, all patients with AS had been treated with GOL, known to strongly suppress VEGF levels[19], whereas about 3% of the German Spondyloarthritis Inception Cohort (GESPIC) patients, a large proportion of whom had axial spondyloarthritis, had been exposed to TNF antagonists[13].

Our findings are consistent with current knowledge on AS pathogenesis, i.e., inflammation and new bone formation appear to be partially uncoupled (Figure 1). While angiogenesis is involved in early/active disease, once inflammation is largely quelled by TNF antagonism, angiogenesis is also stopped and VEGF levels drop. However, bone formation through syndesmophytes, although initially stimulated by inflammation, continues for several years, as was also

Table 2. Spearman correlation analysis of serum VEGF levels (pg/ml) and the ASspiMRI-a scores.

ASspiMRI-a Timepoint	Biomarker/timepoint	Patients, n	r_s	p*
Baseline score	VEGF at baseline	67	0.14	1.000
Week 14				
Score	VEGF at baseline	69	0.14	1.000
	VEGF at Week 14	69	0.21	1.000
	VEGF change at Week 14	67	0.13	1.000
Change from baseline	VEGF at baseline	63	–0.11	1.000
	VEGF at Week 14	63	0.11	1.000
	VEGF change at Week 14	**63**	**0.50**	**0.001**
Week 104				
Score	VEGF at baseline	53	0.33	0.255
	VEGF at Week 14	53	0.28	0.713
	VEGF change at Week 14	52	–0.21	1.000
	VEGF at Week 104	40	0.24	1.000
	VEGF change at Week 104	33	–0.33	1.000
Change from baseline	VEGF at baseline	49	–0.04	1.000
	VEGF at Week 14	49	0.07	1.000
	VEGF change at Week 14	49	0.22	1.000
	VEGF at Week 104	37	0.02	1.000
	VEGF change at Week 104	33	0.05	1.000

* Adjusted for multiplicity of testing through the Bonferroni method. Significant correlations are shown in bold face. VEGF: vascular endothelial growth factor; ASspiMRI-a: Ankylosing Spondylitis spine Magnetic Resonance Imaging activity; r_s: Spearman correlation coefficients.

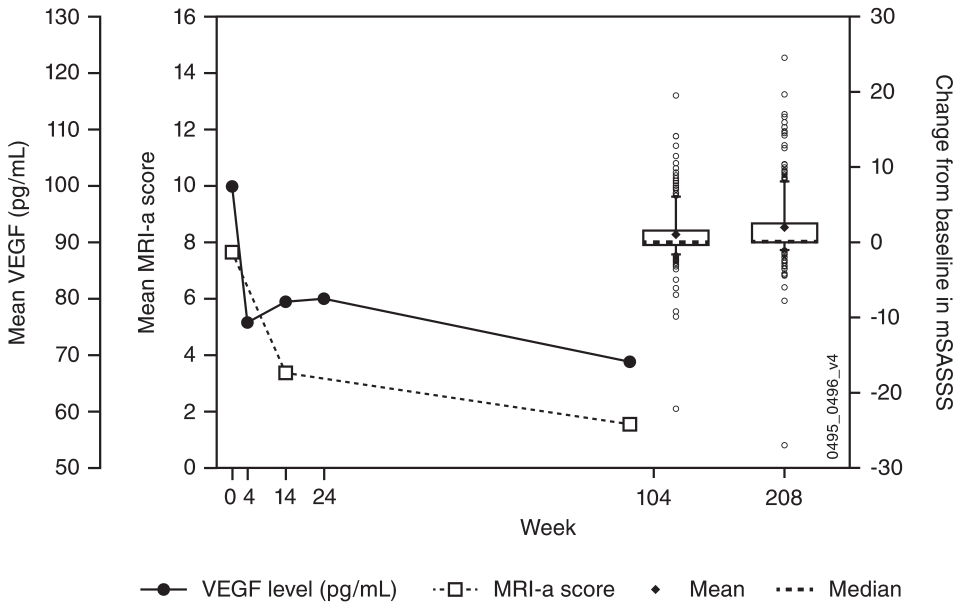

Figure 1. Mean serum VEGF levels, MRI-a scores, and changes in mSASSS over time. VEGF: vascular endothelial growth factor; MRI-a: ankylosing spondylitis spine magnetic resonance imaging-activity; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score.

observed in the GO-RAISE study[8]. Per the EASIC imaging data, the combination of an inflammatory lesion with a fat MRI signal most commonly yielded new bone formation[22]. Although this particular pathology requires further study, it does not appear to involve increases in VEGF serum levels.

While an advantage of our study may be the homogeneity of an active AS population, our study's smaller sample size and longer disease duration relative to the GESPIC needs to be taken into account when interpreting and comparing the data. Conversely, we analyzed serial VEGF measurements within the same patients, while the GESPIC study did not.

Thus, results presented herein suggest VEGF serum levels

do not predict new bone formation in patients with AS receiving TNF antagonists.

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APPENDIX 1. Baseline patient and disease characteristics by subsequent mSASSS change at Week 104 among patients with mSASSS and VEGF data through Week 104. Values are % (n/N) or median (mean ± SD) unless otherwise specified.

Baseline Characteristics	mSASSS Change at Week 104		p*
	≥ 2	< 2	
Patients, n	23	86	
Male	78.3 (18/23)	66.3 (57/86)	0.2706
Age, yrs	41.0 (44.0 ± 13.98)	40.0 (40.6 ± 11.69)	0.2637
Duration of AS diagnosis, yrs	9.6 (11.9 ± 10.66)	5.3 (9.0 ± 9.50)	0.1957
HLA-B27–positive	82.6 (19/23)	79.1 (68/86)	0.7072
CRP, mg/dl	2.2 (2.4 ± 1.84)	1.0 (1.5 ± 1.51)	0.0048
PtGA of disease, 0–10	7.5 (7.5 ± 1.71)	7.2 (7.0 ± 1.71)	0.1885
BASDAI score, 0–10	7.0 (7.0 ± 1.50)	6.7 (6.8 ± 1.42)	0.5167
BASFI score, 0–10	6.9 (6.8 ± 1.94)	5.9 (5.5 ± 2.16)**	0.0067
BASMI score, 0–10	5.0 (5.5 ± 1.78)	3.0 (3.3 ± 2.01)	< 0.0001
mSASSS	15.3 (22.1 ± 16.39)	2.6 (10.7 ± 18.09)	< 0.0001

* P value for comparison of patients with mSASSS change from baseline to Week 104 ≥ 2 vs < 2. ** n = 85. mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; VEGF: vascular endothelial growth factor; AS: ankylosing spondylitis; CRP: C-reactive protein; PtGA: patient's global assessment; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index.