Evaluation of Serum Biomarkers Associated with Radiographic Progression in Methotrexate-naive Rheumatoid Arthritis Patients Treated with Methotrexate or Golimumab

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ABSTRACT. ***Objective.*** To evaluate associations between biomarkers and radiographic progression in methotrexate (MTX)-naive patients with rheumatoid arthritis (RA) treated with MTX or golimumab, a tumor necrosis factor inhibitor (with or without MTX).

Methods. Serum samples from 152 MTX-naive adults with active RA who received placebo + MTX (n = 37) or golimumab (combined 50 mg + MTX or 100 mg ± MTX; n = 115) were analyzed for selected markers of inflammation and bone/cartilage turnover. One hundred patients were randomly selected for additional protein profiling using multianalyte profiles (HumanMap v1.6, Rules Based Medicine). Radiographs at baseline, Week 28, and Week 52 were scored using van der Heijde-Sharp (vdH-S) methodology. Correlations were assessed between biomarker levels (baseline and change at Week 4) and joint space narrowing, erosion, and total vdH-S scores (changes at Weeks 28 and 52). Statistical significance was defined as a correlation coefficient with an absolute value ≥ 0.3 and $p < 0.05$.

Results. Biomarker correlations with changes in vdH-S scores at Week 28 and/or 52 were observed predominantly in the placebo + MTX group and rarely in the combined golimumab treatment group. Changes in epidermal growth factor (EGF) and CD40 ligand (CD40L) at Week 4 were positively correlated with changes in total vdH-S scores at Weeks 28 and 52 in the placebo + MTX group.

Conclusion. These preliminary findings indicate that EGF and CD40L may have utility in monitoring MTX-treated patients with RA who are more likely to have radiographic progression as measured by increases in vdH-S scores. (First Release March 1 2013; J Rheumatol 2013;40:590–8; doi:10.3899/jrheum.120889)

Key Indexing Terms:

TUMOR NECROSIS FACTOR | METHOTREXATE | GOLIMUMAB
RADIOGRAPHIC PROGRESSION | BIOMARKERS | RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic disease characterized by joint inflammation, damage to articular cartilage, and bone erosions. Sustained RA disease activity has been shown to be directly related to radiographic progression[1], much of which has been shown to occur within the first year of disease[2,3]. Therefore, identification of patients with newly diagnosed RA who have a high risk of aggressive disease, and presumed subsequent radiographic progression, could aid in advancing their treatment more quickly from conventional first-line disease-modifying antirheumatic drugs such as methotrexate (MTX) to biologic therapies, such as tumor necrosis factor (TNF) inhibitors, that have been shown to be more effective than MTX monotherapy in inhibiting radiographic progression[4]. In 2 trials of patients with RA (ASPIRE[5] and TEMPO[6]), elevated C-reactive protein (CRP) level and erythrocyte sedimentation rate were predictive of radiographic progression among the subset of patients with the worst radiographic progression after 1 year. In a separate study, levels of matrix metalloproteinase (MMP)-3 and C-telopeptide of type II collagen were correlated with radiographic progression in patients with RA[7]. In addition, the presence of anticitrullinated protein antibodies (ACPA) in early RA has been shown to be a strong predictor of later radiographic progression[8,9]. Rheumatoid factor (RF)

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may also be associated with radiographic progression, particularly erosions, although this association may also be explained by RF-positive patients generally having more severe disease than RF-negative patients[10].

Golimumab is a human anti-TNF-α monoclonal antibody approved in the United States[11], Europe, and elsewhere for treatment of RA, psoriatic arthritis, and ankylosing spondylitis. In a study of patients with active RA despite prior MTX therapy (the GO-FORWARD trial), those who received golimumab plus MTX had significant improvements in the signs and symptoms of RA as measured by the American College of Rheumatology (ACR) response criteria and 28-joint count Disease Activity Score (DAS28) through Week 24 when compared with placebo plus MTX[12]. Patients who received golimumab with or without MTX had decreases in a variety of serum biomarkers at Week 4 compared with those who received placebo plus MTX[13]. Additionally, patients who responded to golimumab treatment as defined by the ACR and DAS28 response criteria exhibited a distinct biomarker profile when compared with nonresponders[13].

In the GO-BEFORE trial, golimumab therapy was evaluated in MTX-naive patients with active RA. Through Week 24, treatment with golimumab reduced the signs and symptoms of RA in this patient population[14]. At Week 52, radiographic progression was significantly greater in patients treated with placebo plus MTX than in patients treated with golimumab plus MTX[15].

We report the findings of a substudy of the GO-BEFORE trial that was performed to determine whether specific biomarkers were associated with radiographic progression in MTX-naive patients with RA given MTX monotherapy or golimumab treatment.

MATERIALS AND METHODS

Patient population and study design. The patient population and study design of the multicenter, randomized, placebo-controlled phase III GO-BEFORE trial have been described[14]. All patients provided written informed consent before undergoing study-related procedures. Study identifiers are as follows: NCT00264537 and EudraCT 2004-003295-10.

Overall, 637 patients were randomly assigned (1:1:1:1) to receive placebo plus MTX (MTX monotherapy), golimumab 100 mg plus placebo, golimumab 50 mg plus MTX, or golimumab 100 mg plus MTX. A subset of 152 patients participated in the pharmacodynamic substudy of serum biomarkers. Patients received subcutaneous injections of placebo or golimumab at baseline and every 4 weeks. At Week 28, patients who had < 20% improvement from baseline in swollen and tender joints entered early escape in a double-blind fashion. Patients entering early escape who were initially assigned to placebo plus MTX switched from placebo injections to golimumab 50 mg, patients who initially received golimumab 100 mg plus placebo switched from placebo to MTX, and patients who initially received golimumab 50 mg plus MTX had their golimumab dose increased to 100 mg. No medication changes were allowed for patients who were already receiving golimumab 100 mg plus MTX, whether they met the early escape criteria or not.

Radiographic assessments. Radiographs of the hands and feet were obtained at baseline, Week 28, and Week 52. Radiographs were scored by 2 independent readers using the van der Heijde modified Sharp (vdH-S) score[2,16]. For the purpose of this analysis, progressors were defined as patients having a change from baseline in total vdH-S score > 0.5 units at Week 28. This definition of radiographic progression (change in total vdH-S > 0.5) is a commonly used threshold in studies of patients with inflammatory arthritides[17,18,19].

Biomarker analyses. Serum samples for markers of inflammation and bone/cartilage turnover were obtained at baseline and at Weeks 4, 24, and 52 and analyzed for 152 patients for whom all scheduled biomarker samples were collected through at least the Week 24 visit. Two different types of biomarker analyses were conducted. Individual assays of inflammatory markers [CRP, interleukin 6 (IL-6), IL-8, intracellular cell adhesion molecule-1 (ICAM-1), MMP-3, TNF-α, and vascular endothelial growth factor (VEGF)] and markers of bone and cartilage turnover [bone alkaline phosphatase (BAP), type II collagen degradation marker, deoxypyridinoline crosslink, hyaluronic acid, osteocalcin, procollagen type 1 N-terminal, and peptide transduction domain] were specifically chosen. In addition, a broader analysis using multianalyte profiles (HumanMap v1.6, Rules Based Medicine; http://rulesbasedmedicine.com) was performed on serum samples from 100 patients randomly selected from the biomarker substudy population who had complete sample collection at all 4 biomarker timepoints (baseline and Weeks 4, 24, and 52). Ninety-two markers (88 markers standard in HumanMap v1.6 plus 4 additional markers: glutathione S transferase α, IL-17, IL-18, and IL-23 p19) were included in this profiling analysis. Some markers (ICAM-1, IL-6, IL-8, MMP-3, TNF-α, and VEGF) were included in both analyses and the data were evaluated as if these were independent analytes.

Statistical analysis. Data for all 3 golimumab treatment groups were combined for comparison with the MTX monotherapy group in all analyses. Data from patients who entered early escape at Week 28 were included in the Week 52 correlation analyses. Linear extrapolation was used to impute vdH-S scores derived from radiographs obtained at an early escape visit. Biomarkers were excluded from this analysis if more than 20% of the values for any given analyte were below the lower limit of quantification.

A heat map was generated to visualize significant fold changes at Weeks 4 and 24 in the various markers relative to baseline levels in the placebo plus MTX group and in the combined golimumab group. In both the MTX monotherapy group and the combined golimumab group, the associations between serum biomarkers (baseline and change from baseline to Week 4) and any change from baseline (> 0 or < 0) in joint space narrowing (JSN), erosion, and total vdH-S scores at Weeks 28 and 52 were assessed by generation of Spearman's correlation coefficients (R) and p values using Fisher's Z-transformation test. In addition, a posthoc analysis was performed to investigate possible correlations between baseline ACPA and RF status with changes in radiographic progression measures at Weeks 28 and 52. A significant correlation was predefined by a p value < 0.05 and an absolute R value ≥ 0.3. Scatterplots were used to visualize the trends between radiographic progression, defined as an increase from baseline of > 0.5 in the total vdH-S, and biomarkers of interest in progressors and nonprogressors. Regression lines were added to display the linear trends between changes in these biomarkers and vdH-S scores.

RESULTS

Baseline demographic and disease characteristics. Of 152 patients included in the biomarker substudy, 37 were randomly assigned to receive MTX monotherapy (placebo plus MTX) and 115 received golimumab (with or without MTX). Baseline demographic characteristics were similar between the placebo plus MTX group and the combined golimumab group (Table 1). In general, patients in the combined golimumab group appeared to have more

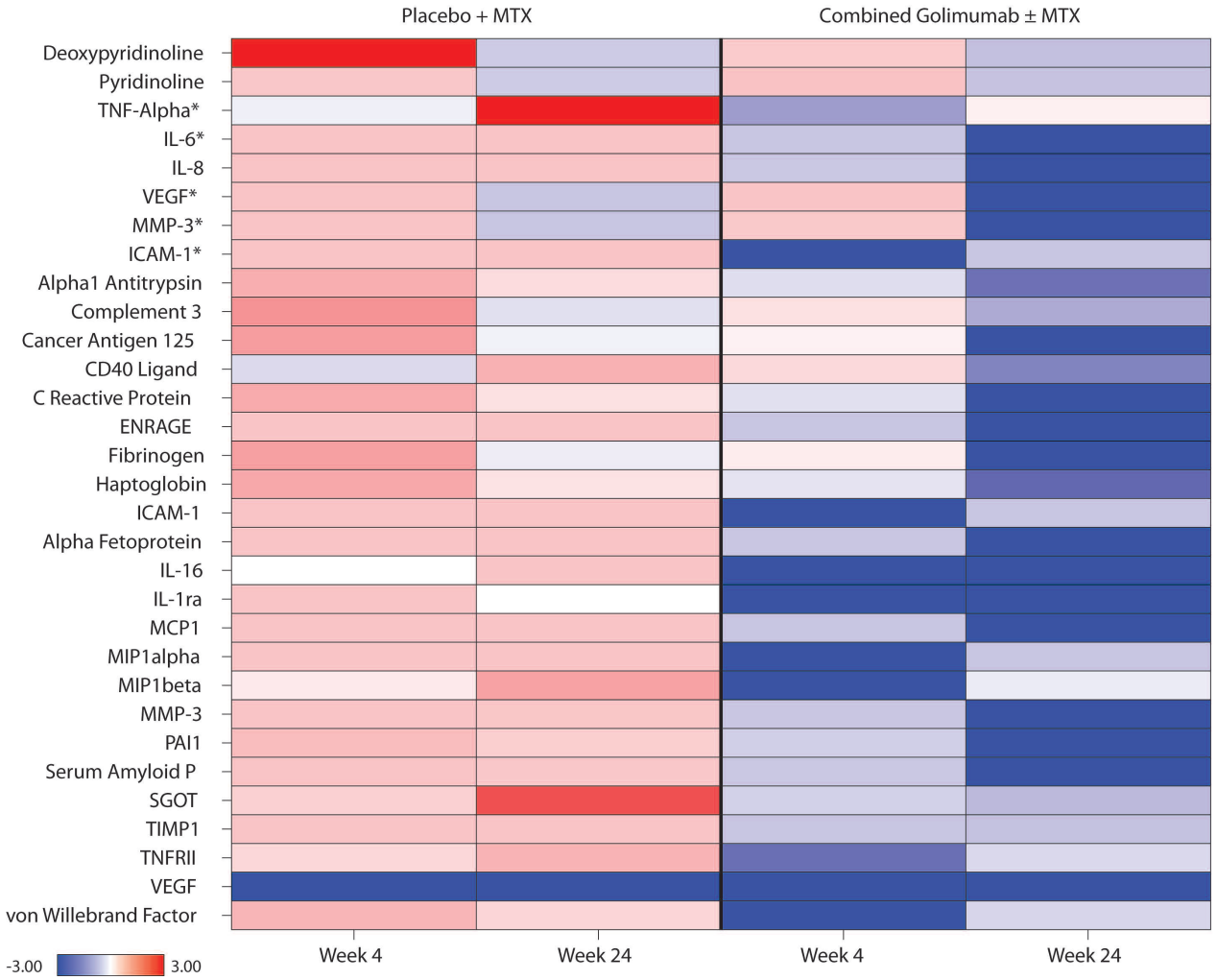

Figure 1. Heat map of biomarkers with significant fold changes from baseline to Week 4 or Week 24 identified in either the placebo + MTX group or the combined golimumab with/without MTX group. *Individual assays. ICAM-1: intracellular adhesion molecule-1; IL: interleukin; IL-1ra: IL-1 receptor antagonist; MIP1: macrophage inflammatory protein; MCP1: monocyte chemotactic protein 1; MMP-3: matrix metalloproteinase-3; MTX: methotrexate; PAI1: plasminogen activator inhibitor 1; SGOT: serum glutamic oxaloacetic transaminase; TIMP1: tissue inhibitor of metalloproteinases 1; TNF: tumor necrosis factor; TNFRII: TNF receptor II; VEGF: vascular endothelial growth factor. ENRAGE: extracellular newly identified receptor for advanced glycation end-products-binding protein.

extensive structural damage (mean vdH-S score 19.9 vs 12.6), slightly longer mean disease duration (3.8 vs 2.4 yrs), and slightly less active inflammation (mean CRP 2.1 vs 2.5 mg/dl) at baseline compared, respectively, with patients in the placebo plus MTX group, although the median values were similar between treatment groups for disease duration and CRP. Comparable demographic results were seen between the biomarker substudy and the overall GO-BEFORE study population (Table 1).

Demographic comparison of total vdH-S score progressors and nonprogressors. Among the 152 substudy patients, 14 of 37 patients (37.8%) in the placebo plus MTX group and 24 of 115 patients (20.9%) in the combined golimumab group experienced an increase > 0.5 in the total vdH-S score from baseline to Week 28 and were classified as progressors (Table 2). Patients with an increase ≤ 0.5 in the total vdH-S score from baseline to Week 28 were classified as nonprogressors. Within each of the treatment groups, patient demographic data were comparable between progressors and nonprogressors; however, some differences were noted in race and disease characteristics. Mean serum CRP level at baseline was significantly higher in progressors than nonprogressors in the MTX monotherapy group (3.6 vs 1.8 mg/dl; $p < 0.05$). In the combined golimumab group, the mean CRP level at baseline was numerically higher for progressors than for nonprogressors (2.7 vs 1.9), but this difference was not statistically significant. Within both groups, progressors appeared to have a longer disease duration and more extensive radiographic damage at baseline compared with nonprogressors, although these differences were not statistically significant.

Changes in biomarkers from baseline to Weeks 4 and 24. Of

Table 1. Baseline demographic and disease characteristics for the overall study population and for patients in the biomarker substudy.

Characteristic	Placebo + MTX	Combined Golimumab ± MTX
Overall GO-BEFORE population		
Patients, n	160	477
Age, yrs		
Mean (SD)	48.6 (12.9)	49.8 (12.1)
Median (IQR)	50.0 (40.5, 57.0)	50.0 (41.0, 58.0)
Female, n (%)	134 (83.8)	394 (82.6)
Race, n (%)		
Asian	25 (15.6)	92 (19.3)
Black	6 (3.8)	6 (1.3)
White	114 (71.3)	347 (72.7)
Other	15 (9.4)	32 (6.7)
Disease duration, yrs		
Mean (SD)	2.9 (4.8)	3.7 (5.8)
Median (IQR)	1.2 (0.5, 3.2)	1.3 (0.5, 4.3)
CRP, mg/dl		
Mean (SD)	2.6 (3.3)	2.5 (3.1)
Median (IQR)	1.4 (0.6, 3.3)	1.3 (0.5, 3.4)
Rheumatoid factor-positive, n (%)	130 (81.3)	377 (79.0)
ACPA-positive, n (%)	121 (75.6)	347 (72.7)
Oral corticosteroid use, n (%)	83 (51.9)	249 (52.2)
vdH-S score (0–448)		
Mean (SD)	19.7 (35.4)	19.1 (32.9)
Median (IQR)	5.3 (2.0, 18.1)	6.0 (2.0, 21.8)
Biomarker substudy population		
Patients, n	37	115
Age, yrs		
Mean (SD)	48.1 (11.6)	47.7 (12.5)
Median (IQR)	51.0 (39.0, 57.0)	49.0 (39.0, 55.0)
Female, n (%)	32 (86.5)	95 (82.6)
Race, n (%)		
Asian	6 (16.2)	20 (17.4)
Black	1 (2.7)	0 (0.0)
White	26 (70.3)	83 (72.2)
Other	4 (10.8)	12 (10.4)
Disease duration, yrs		
Mean (SD)	2.4 (3.8)	3.8 (6.6)
Median (IQR)	1.2 (0.6, 2.7)	1.3 (0.6, 3.3)
CRP, mg/dl		
Mean (SD)	2.5 (2.6)	2.1 (2.3)
Median (IQR)	1.5 (0.6, 2.7)	1.3 (0.5, 2.7)
Rheumatoid factor-positive, n (%)	29 (78.4)	94 (81.7)
ACPA-positive, n (%)	28 (75.7)	94 (81.7)
Oral corticosteroid use, n (%)	27 (73.0)	81 (70.4)
vdH-S score (0–448)		
Mean (SD)	12.6 (30.6)	19.9 (42.8)
Median (IQR)	3.5 (2.0, 10.5)	5.0 (2.0, 16.0)

ACPA: anticitrullinated protein antibodies; CRP: C-reactive protein; IQR: interquartile range; MTX: methotrexate; vdH-S: van der Heijde-Sharp score.

the 99 markers evaluated, 31 increased or decreased significantly from baseline at Week 4 or 24 in either the placebo plus MTX group or the combined golimumab group (Figure 1). Within the MTX monotherapy group, few of these markers decreased from baseline, and most increased slightly. However, in the combined golimumab group, several markers decreased significantly from baseline to Week 4, and additional markers decreased significantly from baseline to Week 24. Of note, VEGF levels (HumanMap assay) decreased significantly from baseline at Weeks 4 and 24 in both treatment groups.

Evaluation of the relationship between serum biomarkers and radiographic progression. At both Week 28 and Week 52, significant correlations between biomarker levels (baseline and change at Week 4) and changes in vdH-S scores (JSN, erosion, or total) were observed primarily

Table 2. Baseline demographic and disease characteristics of progressors and nonprogressors. Progressors were defined as patients with a change from baseline in total van der Heijde-Sharp (vdH-S) score > 0.5 at Week 28.

Characteristic	Placebo + MTX		Combined Golimumab ± MTX	
	No Progression	Progression	No Progression	Progression
Patients, n	23	14	91	24
Age, yrs				
Mean (SD)	49.4 (12.0)	46.1 (11.0)	47.1 (12.5)	50.0 (12.9)
Median (IQR)	52.0 (40.0, 57.0)	46.0 (37.0, 58.0)	48.0 (38.0, 54.0)	49.0 (40.5, 59.0)
Female, n (%)	20 (87.0)	12 (85.7)	74 (81.3)	21 (87.5)
Race, n (%)				
Asian	4 (17.4)	2 (14.3)	16 (17.6)	4 (16.7)
Black	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
White	19 (82.6)	7 (50.0)	68 (74.7)	15 (62.5)
Other	0 (0.0)	4 (28.6)	7 (7.7)	5 (20.8)
CRP, mg/dl				
Mean (SD)	1.8 (2.1)	3.6 (2.9)*	1.9 (2.0)	2.7 (3.1)
Median (IQR)	1.1 (0.4, 1.8)	2.7 (0.9, 4.4)	1.2 (0.5, 2.4)	1.8 (0.5, 3.6)
Disease duration, yrs				
Mean (SD)	1.9 (1.7)	3.2 (5.9)	3.2 (4.9)	5.9 (10.8)
Median (IQR)	1.2 (0.5, 3.2)	1.4 (0.6, 2.7)	1.1 (0.6, 3.3)	1.8 (0.9, 5.8)
vdH-S score (0–448)				
Mean (SD)	8.1 (16.1)	20.0 (45.4)	16.6 (34.2)	32.7 (65.6)
Median (IQR)	3.0 (1.5, 6.0)	6.0 (3.0, 12.0)	4.1 (2.0, 12.5)	9.8 (3.5, 41.8)

* $p < 0.05$. CRP: C-reactive protein; IQR: interquartile range; MTX: methotrexate.

within the placebo plus MTX group and rarely observed within the combined golimumab treatment group (Table 3). In the placebo plus MTX group, baseline levels of α-2 macroglobulin and VEGF (individual assay) were positively correlated with changes in erosion scores at Week 28. Additionally, baseline levels of BAP and haptoglobin were positively correlated with changes in JSN scores at Week 28. Changes from baseline to Week 4 in CD40 ligand (CD40L), epidermal growth factor (EGF), and MMP-3 (individual assay) levels were positively correlated with changes in total vdH-S scores at Week 28; changes in EGF levels from baseline to Week 4 were also positively correlated with changes in erosion scores at Week 28 (Table 3).

Among patients in the placebo plus MTX group, baseline levels of deoxypyridinoline and IL-1 receptor antagonist (IL-1ra) were negatively correlated with changes in erosion and total vdH-S scores at Week 52 (Table 3). Baseline levels of type 2 collagenase long neoepitope (COL 2-3/4C LN) and changes from baseline to Week 4 in COL 2-3/4C LN levels were inversely correlated with changes in total vdH-S scores at Week 52; changes from baseline to Week 4 in COL 2-3/4C LN were also inversely correlated with changes in JSN scores. Changes in MMP-3 levels (individual assay) at Week 4 were positively correlated with changes in JSN scores at Week 52. Of note, changes in CD40L at Week 4 positively correlated with changes in all of the radiographic progression measures (erosion, JSN, and total vdH-S scores) at Week 52, and changes in EGF levels at Week 4 positively correlated with changes in erosion and total vdH-S scores.

Within the combined golimumab group, few significant correlations were observed. Baseline IL-1ra levels were positively correlated with changes in erosion (Week 28) and total vdH-S scores (Week 52), and changes in EGF at Week 4 were negatively correlated with changes in JSN scores at Week 52 (Table 3).

Interestingly, CRP levels (baseline and change at Week 4) were not significantly correlated with changes in erosion, JSN, or total vdH-S scores at either Week 28 or Week 52 in either treatment group (data not shown). To further explore the potential relationship between changes in CRP and radiographic progression, a separate correlation analysis was performed with CRP levels (baseline and change at Week 4) and changes in vdH-S score at Weeks 28 and 52 for patients classified as progressors or nonprogressors. No significant correlations were observed for progressors or nonprogressors in the MTX monotherapy group in this analysis. In the combined golimumab group, the only significant correlation for progressors was between baseline CRP level and changes in vdH-S score at Week 52 ($r = 0.513$; $p = 0.0352$), and no significant correlations were observed for CRP in nonprogressors (data not shown).

To further evaluate other markers previously established to be associated with radiographic progression, a similar analysis was conducted looking at the relationship of radiographic progression with ACPA and RF status at baseline. A positive ACPA status at baseline was significantly associated with changes in erosion and total vdH-S scores at Week 28 in the MTX monotherapy group only; however, there were no significant correlations between baseline ACPA status and changes in vdH-S scores (JSN,

Table 3. Biomarkers significantly correlated* with structural damage endpoints at Weeks 28 and 52.

Biomarker Timepoint	Biomarker	Efficacy Measure	Placebo + MTX N	Placebo + MTX R	Placebo + MTX p	Combined Golimumab ± MTX N	Combined Golimumab ± MTX R	Combined Golimumab ± MTX p
		Change at Week 28 in:						
Baseline	α-2 macroglobulin	Erosion score	23	0.480	0.021	71	–0.057	0.635
	BAP	JSN score	36	0.447	0.006	109	–0.016	0.870
	Haptoglobin	JSN score	23	0.486	0.019	70	–0.014	0.907
	IL-1ra	Erosion score	23	–0.311	0.149	69	0.246	0.042
	VEGF**	Erosion score	34	0.522	0.002	105	–0.017	0.863
Change at Week 4	CD40L	Total vdH-S score	23	0.532	0.009	71	–0.007	0.956
	EGF	Erosion score	23	0.479	0.021	70	–0.045	0.714
	EGF	Total vdH-S score	23	0.492	0.017	70	–0.154	0.203
	MMP-3**	Total vdH-S score	36	0.374	0.025	111	–0.062	0.517
		Change at Week 52 in:						
Baseline	COL 2-3/4C LN	Total vdH-S score	35	–0.448	0.007	103	–0.051	0.607
	Deoxypyridinoline	Erosion score	33	–0.483	0.004	102	–0.063	0.532
	Deoxypyridinoline	Total vdH-S score	33	–0.354	0.043	102	0.054	0.592
	IL-1ra	Erosion score	21	–0.449	0.041	64	0.197	0.118
	IL-1ra	Total vdH-S score	21	–0.452	0.040	64	0.247	0.049
Change at Week 4	CD40L	Erosion score	21	0.606	0.004	66	0.083	0.507
	CD40L	JSN score	21	0.541	0.011	66	–0.143	0.252
	CD40L	Total vdH-S score	21	0.656	0.001	66	0.030	0.810
	COL 2-3/4C LN	JSN score	35	–0.433	0.009	103	0.097	0.328
	COL 2-3/4C LN	Total vdH-S score	35	–0.367	0.030	103	0.107	0.282
	EGF	Erosion score	21	0.460	0.036	65	–0.119	0.344
	EGF	JSN score	21	0.417	0.060	65	–0.272	0.029
	EGF	Total vdH-S score	21	0.471	0.031	65	–0.224	0.072
	MIP1ß	Total vdH-S score	21	0.470	0.032	65	–0.045	0.721
	MMP-3**	JSN score	21	0.460	0.036	66	–0.050	0.688

* Defined as $p < 0.05$ and $R \geq 0.3$ for either placebo + MTX or combined golimumab. ** Individual serum assays. BAP: bone alkaline phosphatase; CD40L: CD40 ligand; COL 2-3/4C LN: type 2 collagenase long neoepitope; EGF: epidermal growth factor; IL-1ra: interleukin 1 receptor antagonist; JSN: joint space narrowing; MIP1ß: macrophage inflammatory protein 1ß; MMP-3: matrix metalloproteinase-3; MTX: methotrexate; vdH-S: van der Heijde-Sharp score; VEGF: vascular endothelial growth factor.

erosion, and total scores) at Week 52. Further, there were no significant correlations in either treatment group between baseline RF status and changes in vdH-S scores (JSN, erosion, and total scores) at Week 28 or 52 (data not shown).

Scatterplots were used to compare changes from baseline to Week 28 in vdH-S scores with changes from baseline to Week 4 in CD40L levels and EGF levels in radiographic progressors and nonprogressors. Although meaningful statistical comparisons could not be conducted because of the limited sample size, trends indicating a positive association between serum levels of CD40L and EGF and radiographic progression were observed in the MTX monotherapy group (Figures 2 and 3) but were not evident for golimumab-treated patients. Scatterplots created for other markers that correlated with radiographic progression did not show any notable trends for progressors or nonprogressors (data not shown).

DISCUSSION

As part of the multicenter, randomized, placebo-controlled phase III GO-BEFORE trial[14], serum samples from 152 MTX-naive adults with active RA, who received subcutaneous injections of placebo plus MTX or golimumab with or without MTX, were analyzed for markers of inflammation and bone/cartilage turnover. Baseline demographic and disease characteristics of the substudy population were generally consistent with those observed in the overall GO-BEFORE trial cohort[14]. In this analysis, a smaller proportion of patients in the combined golimumab group had radiographic progression > 0.5 vdH-S units through Week 52 compared with the MTX monotherapy group. These results are consistent with findings from the overall population, in which patients who received golimumab plus MTX had significantly less radiographic progression compared with those who received MTX monotherapy[15].

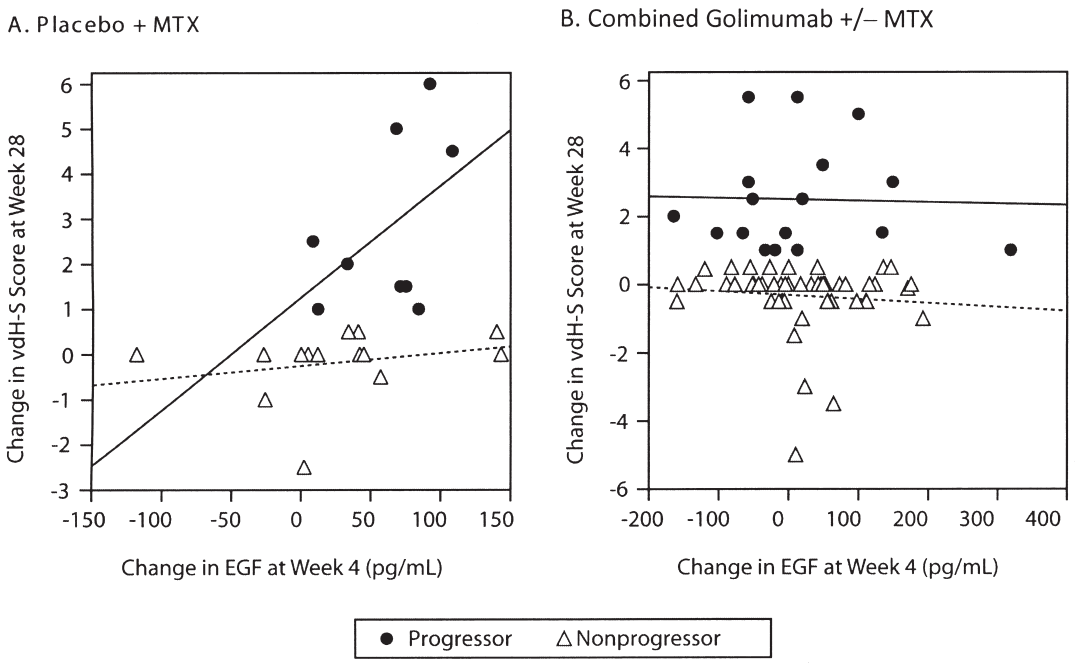

Figure 2. Comparison of change in van der Heijde-Sharp (vdH-S) score (baseline to Week 28) with change in EGF levels (baseline to Week 4) for structural damage progressors and nonprogressors in patients randomized to treatment with placebo + MTX (panel A) or combined golimumab with/without MTX (panel B). Radiographic progression was defined as increase from baseline > 0.5 in total vdH-S score. EGF: endothelial growth factor; MTX: methotrexate.

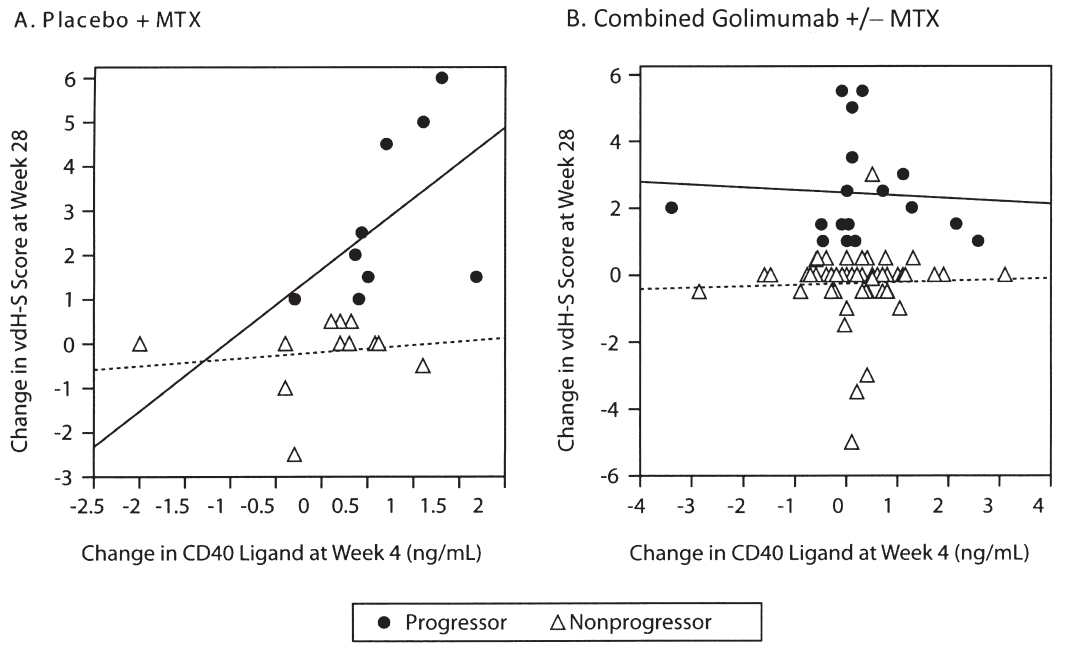

Figure 3. Comparison of change in van der Heijde-Sharp (vdH-S) score (baseline to Week 28) with change in CD40 ligand levels (baseline to Week 4) for structural damage progressors and nonprogressors in patients randomized to treatment with placebo + MTX (panel A) or combined golimumab with/without MTX (panel B). Radiographic progression was defined as an increase from baseline > 0.5 in the total vdH-S score. MTX: methotrexate.

In our assessment of the relationship between biomarker levels and radiographic progression in MTX-naive patients with RA, significant correlations were observed predominantly in the MTX monotherapy group. These relationships were most apparent using a comparison of change from baseline relative to 4 weeks after study initiation, indicating

that a relatively short period of biomarker evaluation could be useful in predicting much longer-term radiographic progression. The relative lack of such relationships in the combined golimumab group likely reflects the disease modulation and thus the inhibition of radiographic progression following initiation of golimumab therapy.

Unlike the ASPIRE[5] and TEMPO[6] trials, CRP levels were not correlated with radiographic progression in either the MTX monotherapy group or the combined golimumab group, although significantly higher CRP levels were observed for the radiographic progressors compared with nonprogressors. Our analysis differed from the ASPIRE and TEMPO results in several important ways. In those analyses, elevated CRP levels at baseline (ASPIRE) or Week 12 (TEMPO) were associated with greater radiographic progression. Our correlation analysis included all baseline levels of CRP and changes in CRP from baseline to Week 4, and did not select for only those patients with elevated CRP levels. In addition, our analyses showed the strongest correlations between biomarker changes from baseline to Week 4 and radiographic changes, and were not limited to comparisons with only baseline biomarkers. Our study also examined all changes in vdH-S scores and was not limited to only those patients with the highest degree of radiographic progression. In addition, an analysis of ACPA at baseline showed a correlation with erosion scores at Week 28 only in the MTX monotherapy group, which is consistent with previous research demonstrating that ACPA status is a strong predictor of radiographic progression[8,9]. However, this relationship was not maintained at Week 52, and no significant correlations were observed between baseline RF status and radiographic progression. It should, however, be acknowledged that this correlation analysis may have been limited by the relatively small sample sizes evaluated.

Changes in EGF and CD40L levels from baseline to Week 4 were associated with changes in more than 1 radiographic score at Week 52 in the MTX monotherapy group. CD40L levels increased significantly from baseline to Week 24 in the MTX monotherapy group, as indicated in the heat map. However, EGF levels at Weeks 4 and 24 were not changed significantly from baseline in this treatment group despite the correlation that was observed between this marker and radiographic progression. This apparent discrepancy can be explained by the largest changes and radiographic correlations with EGF levels being driven primarily by the 14 patients in the MTX monotherapy group who were classified as progressors, and the changes in EGF levels in this subset were not sufficient to result in significant EGF changes for the entire treatment group.

Both EGF and CD40L are believed to be closely associated with bone remodeling. CD40 ligation of RA synovial fibroblasts starts a cascade resulting in increased osteoclast formation; and both cell types play important roles in bone and cartilage destruction in RA[20]. The EGF and EGF receptor network have recently been implicated in bone remodeling in transgenic mouse models[21] and in regulating aspects of proliferation and differentiation of osteoblasts, chondrocytes, and osteoclasts, parathyroid hormone-mediated bone formation, and cancer metastases[22].

It is acknowledged that this subanalysis of the GO-BEFORE trial is limited by the small sample size, especially given the few patients who had radiographic progression. The substudy was not powered to detect differences among the golimumab treatment groups, thus we were not able to evaluate potential differences in the effects of golimumab monotherapy and combination therapy with MTX on serum biomarkers and radiographic progression in this population. While about 70% of patients in the GO-BEFORE trial had a disease duration ≤ 3 years[14], the trial population was not strictly an early RA cohort, thus limiting the generalizability of the results. Additionally, because of the limited radiographic progression observed through Week 52 among golimumab-treated patients, there were few markers that could be identified as being associated with radiographic progression in these treated patients. Data from the MTX monotherapy group, however, allowed for a more thorough investigation of biomarkers and radiographic progression because of the larger changes in vdH-S scores. Overall, results of this preliminary biomarker study in MTX-naive patients with RA indicate that EGF and CD40L may be useful in identifying newly diagnosed patients with RA who are treated with MTX and are likely to have significant radiographic progression. Additional studies are needed to confirm these results in a larger cohort of patients with RA who are receiving MTX treatment to confirm whether these 2 biomarkers would be useful in monitoring those patients who have radiographic progression. Although this study was not designed to identify prognostic indicators, the results of our analysis can help to provide a foundation for subsequent evaluations of biomarkers and radiographic damage in patients with RA.

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REFERENCES

1. Welsing PM, Landewe RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.
2. van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. Br J Rheumatol 1995;34 Suppl 2:74-8.
3. Bresnihan B. Rheumatoid arthritis: Principles of early treatment. J Rheumatol Suppl. 2002 Nov;66:9-12.
4. Keystone E. Recent concepts in the inhibition of radiographic progression with biologics. Curr Opin Rheumatol 2009;21:231-7.

5. Smolen JS, van der Heijde DM, St. Clair EW, Emery P, Bathon JM, Keystone E, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54:702-10.
6. Weinblatt ME, Keystone EC, Cohen MD, Freundlich B, Li J, Chon Y, et al. Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate. J Rheumatol 2011;38:242-6.
7. Young-Min S, Cawston T, Marshall N, Coady D, Christgau S, Saxne T, et al. Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers. Arthritis Rheum 2007;56:3236-47.
8. Meyer O, Labarre C, Dougados M, Goupille P, Cantagrel A, Dubois A, et al. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. Ann Rheum Dis 2003;62:120-6.
9. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: Diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146:797-808.
10. Aletaha D, Alasti F, Smolen JS. Rheumatoid factor determines structural progression of rheumatoid arthritis dependent and independent of disease activity. Ann Rheum Dis 2012 Jul 13 [E-pub ahead of print].
11. Simponi: Package insert. Horsham, PA: Janssen Biotech Inc.; 2011.
12. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: The GO-FORWARD Study. Ann Rheum Dis 2009;68:789-96.
13. Visvanathan S, Rahman MU, Keystone E, Genovese M, Klareskog L, Hsia E, et al. Association of serum markers with improvement in clinical response measures after treatment with golimumab in patients with active rheumatoid arthritis despite receiving methotrexate: results from the GO-FORWARD study. Arthritis Res Ther 2010;12:R211.
14. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60:2272-83.
15. Emery P, Fleischmann R, van der Heijde D, Keystone EC, Genovese MC, Conaghan PG, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. Arthritis Rheum 2011;63:1200-10.
16. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261-3.
17. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
18. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: Two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443-50.
19. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: Forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum 2007;56:476-88.
20. Lee HY, Jeon HS, Song EK, Han MK, Park SI, Lee SI, et al. CD40 ligation of rheumatoid synovial fibroblasts regulates RANKL-mediated osteoclastogenesis: evidence of NF-kappa B-dependent, CD40-mediated bone destruction in rheumatoid arthritis. Arthritis Rheum 2006;54:1747-58.
21. Guise TA. Breaking down bone: New insight into site-specific mechanisms of breast cancer osteolysis mediated by metalloproteinases. Genes Dev 2009;23:2117-23.
22. Schneider MR, Sibilia M, Erben RG. The EGFR network in bone biology and pathology. Trends Endocrinol Metab 2009;20:517-24.