Serum C-reactive Protein Levels Demonstrate Predictive Value for Radiographic and Magnetic Resonance Imaging Outcomes in Patients with Active Ankylosing Spondylitis Treated with Golimumab

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

ABSTRACT. ***Objective.*** Serum C-reactive protein (CRP) associates with radiographic progression in patients with ankylosing spondylitis (AS) untreated with tumor necrosis factor (TNF) antagonists. We assessed correlations between serum CRP and radiographic progression/magnetic resonance imaging (MRI)-detected inflammation after 2 years of anti-TNF therapy.

Methods. Patients with active AS receiving golimumab (GOL)/placebo through Week 16 (early escape) or Week 24 (crossover by design), followed by GOL through 4 years, had sera/images obtained through Week 208. Lateral spinal radiographs and spinal MRI were scored with the modified Stoke AS Spine Score (mSASSS) and the AS spine MRI activity (ASspiMRI-a) score, respectively. ANOVA assessed differences based on CRP levels and mSASSS progression. The relationships between CRP levels and mSASSS/ASspiMRI-a were assessed by Spearman correlation and logistic regression.

Results. Of the randomized GO-RAISE patients, 299 (84.0%) had pre- and posttreatment spinal radiographs. Larger proportions of patients with Week 104 CRP ≥ 0.5 mg/dl (n = 47) versus < 0.5 mg/dl (n = 236, 40.4% vs 22.9%, p = 0.0121) had mSASSS changes ≥ 2 at Week 104. Across several visits, serum CRP demonstrated weak associations with mSASSS change ($r_s \leq 0.21$, $p < 0.05$, n = 262–293) and moderate associations with ASspiMRI-a change ($r_s = -0.33$ to 0.54, $p < 0.05$, n = 65–89). Higher baseline CRP was associated with increased risk for syndesmophytes at Week 104/Week 208, and large, short-term decreases in CRP from baseline to Week 14/Week 24 also yielded increased syndesmophyte formation risk.

Conclusion. Elevated CRP after 2 years of anti-TNF treatment correlated with greater radiographic progression risk at 4 years. Elevated CRP at baseline or Week 14/Week 24 of anti-TNF treatment weakly predicted subsequent radiographic progression and modestly predicted residual spinal inflammation in patients with AS treated with anti-TNF. Findings are useful regarding new treatment options in patients treated with anti-TNF. ClinicalTrials.gov: NCT00265083. (First Release July 15 2016; J Rheumatol 2016;43:1704–12; doi:10.3899/jrheum.160003)

Key Indexing Terms:
C-REACTIVE PROTEIN RADIOGRAPH MAGNETIC RESONANCE IMAGING
ANKYLOSING SPONDYLITIS TUMOR NECROSIS FACTOR GOLIMUMAB

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Supported by Janssen Research and Development LLC, and Merck/Schering-Plough Research Institute Inc.

J. Braun has received honoraria for talks, advisory boards, paid consultancies, and grants for studies from Janssen Research and Development LLC. X. Baraliakos has received honoraria for talks, advisory boards, paid consultancies, and grants for studies from Janssen. K.G. Hermann has received honoraria for educational lectures from Janssen. S. Xu and B. Hsu are employees of Janssen.

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Accepted for publication May 31, 2016.

Ankylosing spondylitis (AS) is an immune-mediated inflammatory disease mainly affecting the axial skeleton. The initial sacroiliac spinal inflammation that characterizes AS is typically followed by new bone formation, e.g., syndesmophytes and ankylosis, which can markedly diminish physical function and quality of life.

While the introduction of antitumor necrosis factor (anti-TNF) biologic agents can significantly improve the signs and symptoms of AS[1] and reduce magnetic resonance imaging (MRI)-detected spinal inflammation[2,3,4], the effect of such therapy on future radiographic progression is less clear. While studies evaluating etanercept (ETN), infliximab (IFX), and adalimumab did not demonstrate inhibition of radiographic progression after 2 years of therapy[5,6,7], radiographic progression appeared to have slowed after 4 years of IFX anti-TNF therapy[8]. Also, results through 4 years of the phase III, randomized, placebo-controlled GO-RAISE trial of

golimumab (GOL) in AS indicated that the radiographic progression rate remained stable at years 2 and 4 of anti-TNF treatment, with no acceleration of new bone formation[9]. In longer-term assessments of patients with AS, the total duration of anti-TNF treatment was inversely associated with progression; patients who received anti-TNF agents for > 50% of their disease duration had significantly less risk of progression than patients who did not[10].

Given the ultimate goals of AS treatment, i.e., control of disease activity, prevention of radiographic progression, and maintenance of physical function, it would be valuable to have a biomarker that is measured pretreatment or after short-term treatment — one that can either identify patients likely to progress rapidly or reliably predict longterm outcomes. In a cohort of patients with AS not treated with anti-TNF agents, the inflammatory marker C-reactive protein (CRP) has been shown to predict radiographic progression[11,12]. At the same time, serum CRP levels are known to decrease in patients with AS receiving TNF antagonists and demonstrating clinical improvement[13,14]. In a prospective study of MRI-detected inflammation, radiographic progression, and inflammatory biomarkers in patients with axial spondyloarthritis (axSpA) beginning anti-TNF therapy, development of new syndesmophytes and progression in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) were both associated with larger decreases in, and normalization of, CRP levels[15]. To further assess such relationships, we used data from the GO-RAISE trial of GOL in patients with active AS (NCT00265083) to analyze correlations between serum CRP levels during therapy, radiographic progression, and spinal inflammation as detected by MRI.

MATERIALS AND METHODS

Study design and patients. The GO-RAISE protocol was reviewed and approved by each site's institutional review board or independent ethics committee (see Appendix 1), and all patients provided written informed consent. Details of the GO-RAISE patient selection criteria and study design have been described[16,17]. Eligible patients had definite AS according to the modified New York criteria[18] and active disease, as defined by a Bath Ankylosing Spondylitis Disease Activity Index[19] score ≥ 4 and total back pain visual analog scale score ≥ 4 (both on a scale of 0–10 cm).

The GO-RAISE study design is depicted in Figure 1. Patients with active AS enrolled into the phase III, multicenter, randomized, placebo-controlled, double-blind GO-RAISE trial 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. Randomization was stratified by investigational study site and screening CRP level (≤ 1.5 mg/dl, > 1.5 mg/dl). Patients in the placebo group who had < 20% improvement in total back pain and morning stiffness received double-blind early escape treatment at Week 16; thus, the study was fully placebo-controlled from weeks 0 to 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 administration of GOL. At the investigator's discretion, the GOL dose could be increased from 50 mg to 100 mg every 4 weeks or decreased from 100 mg to 50 mg every 4 weeks during the longterm extension[20].

Biomarker assessments. Serum samples collected at weeks 0, 4, 14, 24, and 104 of the GO-RAISE trial were tested for selected biomarkers, including CRP, using an ELISA platform by Quintiles Laboratories. The reference range for this assay was 0.0–0.6 mg/dl, and the lower limit of quantitation was 0.3 mg/dl.

Imaging assessments. Lateral view radiographs of the cervical and lumbar spine were performed at weeks 0, 104, and 208. Radiographs were scored using the mSASSS method[21], 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. The total mSASSS ranged from 0 to 72.

Serial spine MRI scans of the cervical, thoracic, and lumbar spine in the sagittal plane were acquired with the patient in the supine position using 1.5 Tesla scanners and phase array spine or quadrature coils at weeks 0, 14, and 104. Image sequences were scored using the AS spine MRI-activity (ASspiMRI-a) score (range 0–138)[2].

Radiographs and MRI were read by 2 qualified, experienced, and independent readers who were blinded to treatment information, patient identity, and chronology of the images. Further details of radiographic[9] and MRI[3] protocols and scoring have been described.

Statistical analysis. Analyses of imaging data collected through Week 208 used observed data; missing data were not imputed. ANOVA using the van der Waerden ranking methodology were used to assess differences in CRP levels at Week 0 and changes at weeks 14 and 24 between patients with mSASSS change ≥ 2 and those with mSASSS change < 2 at Week 104 and Week 208. Reciprocal analyses assessed the differences in the proportions of patients with mSASSS change ≥ 2 between patients with CRP levels ≤ 0.3 mg/dl versus > 0.3 mg/dl and < 0.5 mg/dl versus ≥ 0.5 mg/dl at Week 104.

The relationships between CRP levels and ASspiMRI-a scores were assessed by the generation of Spearman correlation coefficients (r_s). P values were adjusted for multiplicity of testing using the Bonferroni methods.

Logistic regression analyses were conducted to assess whether CRP levels at various timepoints and baseline factors (age, sex, HLA-B27 status, mSASSS, and smoking status) conferred an increased risk of syndesmophyte formation or radiographic progression from baseline to Week 104 or Week 208. Syndesmophyte formation was defined as having at least 1 vertebral level on radiograph that changed from a score < 2 at baseline to an mSASSS of 2 or 3 at Week 104 or 208, according to at least 1 reader. Radiographic progression was defined as a change of 2 or more units in the mSASSS from baseline to Week 104 or 208.

RESULTS

Analysis groups. The vast majority of 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 262–293 patients with CRP and mSASSS data and 65–89 patients with CRP and ASspiMRI-a data across the timepoints assessed.

About 20%–25% of the patients in each group were initially assigned to placebo. As reported, the demographic and baseline characteristics for the MRI substudy patients were generally consistent with those of the overall GO-RAISE patient population[3]. Assessment of baseline patient and disease characteristics by CRP level at Week 104 indicated more severe and active disease at baseline among patients with CRP levels remaining ≥ 0.5 mg/dl after up to 2 years of GOL therapy (Table 1).

Serum CRP levels and mSASSS. Although statistically significant, Spearman correlation coefficients indicated only weak associations between serum CRP levels (baseline, Week 14, Week 24) and mSASSS (Week 104, Week 208) across the

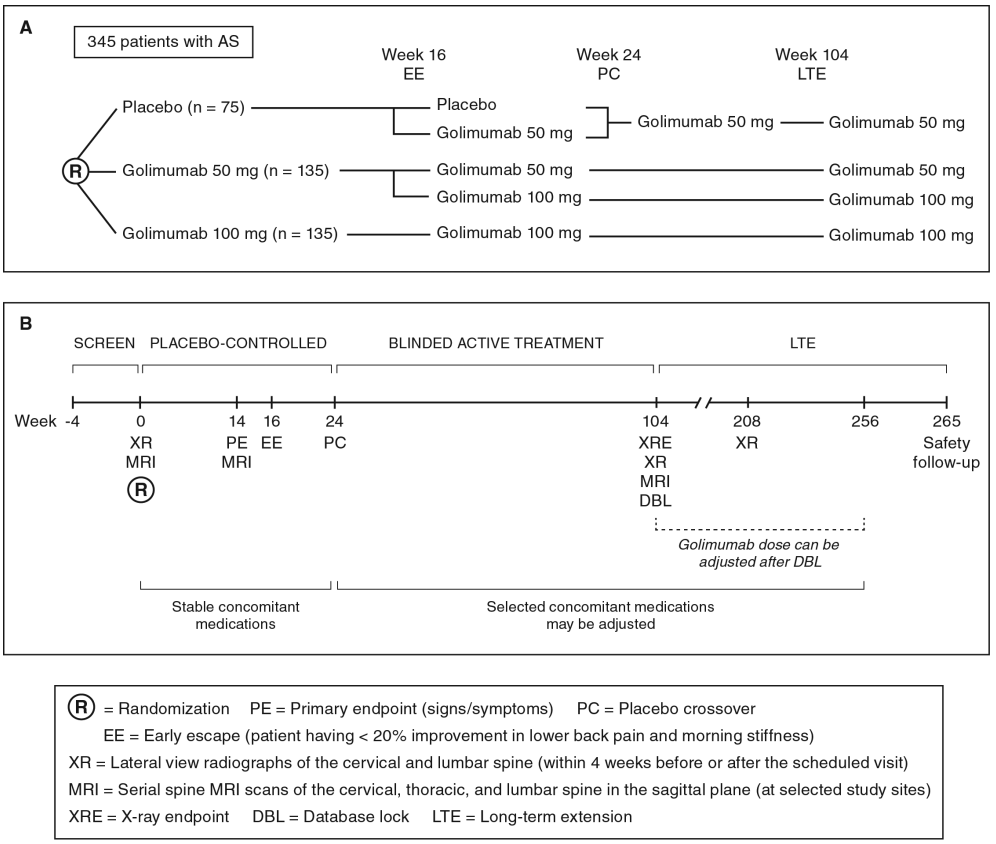


Figure 1. Design of the GO-RAISE study of golimumab in ankylosing spondylitis. AS: ankylosing spondylitis; MRI: magnetic resonance imaging.

assessed timepoints ($r_s \leq 0.21$). However, median baseline CRP levels were higher and median decreases from baseline to Week 14 and/or Week 24 were greater among patients with mSASSS change scores ≥ 2 at Week 104 and Week 208 ($p < 0.05$; Table 2). Consistent with these findings, the median mSASSS change from baseline to Week 104 was significantly greater in patients with CRP levels ≥ 0.5 mg/dl than in those with CRP < 0.5 mg/dl at Week 104 (1.09 vs 0.00, $p = 0.0369$; Figure 2A). Additionally, larger proportions of patients with CRP > 0.3 mg/dl versus ≤ 0.3 mg/dl (34.4% vs 23.4%, $p = 0.0819$) and CRP ≥ 0.5 mg/dl versus < 0.5 mg/dl (40.4% vs 22.9%, $p = 0.0121$) at Week 104 had mSASSS change ≥ 2 at Week 104 (Table 3). We observed no consistent difference between the 50-mg and 100-mg doses of GOL (data not shown).

The relationship between serum CRP levels and mSASSS over time is further detailed in Figure 2B. Significant differences in the mSASSS were observed between patient subgroups defined by CRP levels ≤ 0.3 mg/dl versus ≥ 0.5 mg/dl at baseline (Week 0, $p = 0.0008$) and 4 years (Week 208, $p = 0.0027$).

Further assessment through logistic regression analysis showed a mildly increased risk of syndesmophyte formation at weeks 104 and/or 208 to be associated with baseline mSASSS, age, sex, and greater short-term decreases in serum CRP levels from baseline to Week 14 and Week 24 (Table 4). The association of change in CRP from baseline to Week 14 or 24 with syndesmophyte formation confirmed the finding shown in Table 2, and suggested that a large decrease in CRP with treatment, rather than the actual baseline or post-treatment CRP values, was predictive of future new syndesmophyte formation. In terms of radiographic progression at weeks 104 and 208, only baseline mSASSS was a significant predictor of subsequent damage (Table 4).

Serum CRP levels and ASspiMRI-a. Results of the Spearman correlation analyses indicated a moderate degree of association between serum CRP levels and ASspiMRI-a scores at baseline and Week 14 ($r_s = -0.33$ to 0.54, $p < 0.05$). Baseline CRP levels ($r_s = -0.40$, $p = 0.0177$) and changes in CRP levels at Week 104 ($r_s = 0.37$, $p = 0.0452$) also demonstrated moderate associations with MRI-detected change in disease activity at Week 104 (Table 5).

DISCUSSION

In our investigation, serum biomarker and imaging data from a large trial of patients with AS receiving anti-TNF therapy have been evaluated in a comprehensive and systematic manner. Our data show that serum CRP levels at different

Table 1. Baseline patient and disease characteristics among randomized patients by CRP level at Week 104. For the variables, n/N refers to number of patients with that data/total number of patients.

Baseline Variables	CRP, mg/dl, at Week 104	
	< 0.5	≥ 0.5
Age, yrs, N	231	45
Mean ± SD	39.0 ± 12.24	39.8 ± 11.85
p		0.5928
Male, % (n/N)	74.5 (172/231)	66.7 (30/45)
p		0.2804
BASDAI, 0–10, N	231	45
Mean ± SD	6.5 ± 1.44	6.8 ± 1.72
p		0.1721
BASFI, 0–10, N	229	45
Mean ± SD	4.7 ± 2.36	6.8 ± 1.98
p		< 0.0001
BASMI, 0–10, N	231	45
Mean ± SD	3.3 ± 2.02	4.8 ± 2.38
p		< 0.0001
CRP, mg/dl, N	231	45
Mean ± SD	1.6 ± 1.86	3.1 ± 2.44
p		< 0.0001
AS diagnosis duration, yrs, N	231	45
Mean ± SD	8.5 ± 8.62	10.5 ± 9.75
p		0.2298
HLA-B27+, % (n/N)	86.6 (200/231)	86.7 (39/45)
p		0.9876
PtGA of disease, 0–10, N	230	45
Mean ± SD	6.7 ± 1.75	7.5 ± 1.96
p		0.0063
Yrs since symptoms of SpA first occurred, n	231	45
Mean ± SD	12.5 ± 10.41	17.8 ± 11.75
p		0.0023
mSASSS score, 0–72, N	236	47
Mean ± SD	12.5 ± 16.69	20.8 ± 23.51
p		0.0028

CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; AS: ankylosing spondylitis; PtGA: patient's global assessment; SpA: spondyloarthritis; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

timepoints are associated with radiographic progression in patients treated with anti-TNF agents. This could have important implications, since it may suggest that some patients are in need of more or stronger antiinflammatory treatment with TNF antagonists.

Prior to our report, elevated serum CRP levels have been shown to predict radiographic progression in patients with AS who had been conventionally treated[11,12,22]. Our present analysis shows that changes in serum CRP levels can predict and correlate with radiographic progression in anti-TNF–treated patients, and that the reduction of CRP in such patients correlates with a decrease in spinal inflammation as detected by MRI. In addition, patients whose CRP level was reduced to < 0.5 mg/dl at Week 104 had far less radiographic progression from baseline to Week 104 than did patients whose CRP levels remained ≥ 0.5 mg/dl.

Interestingly, results of logistic regression analysis

Table 2. Median serum CRP levels (mg/dl) through Week 24 and subsequent radiographic progression.

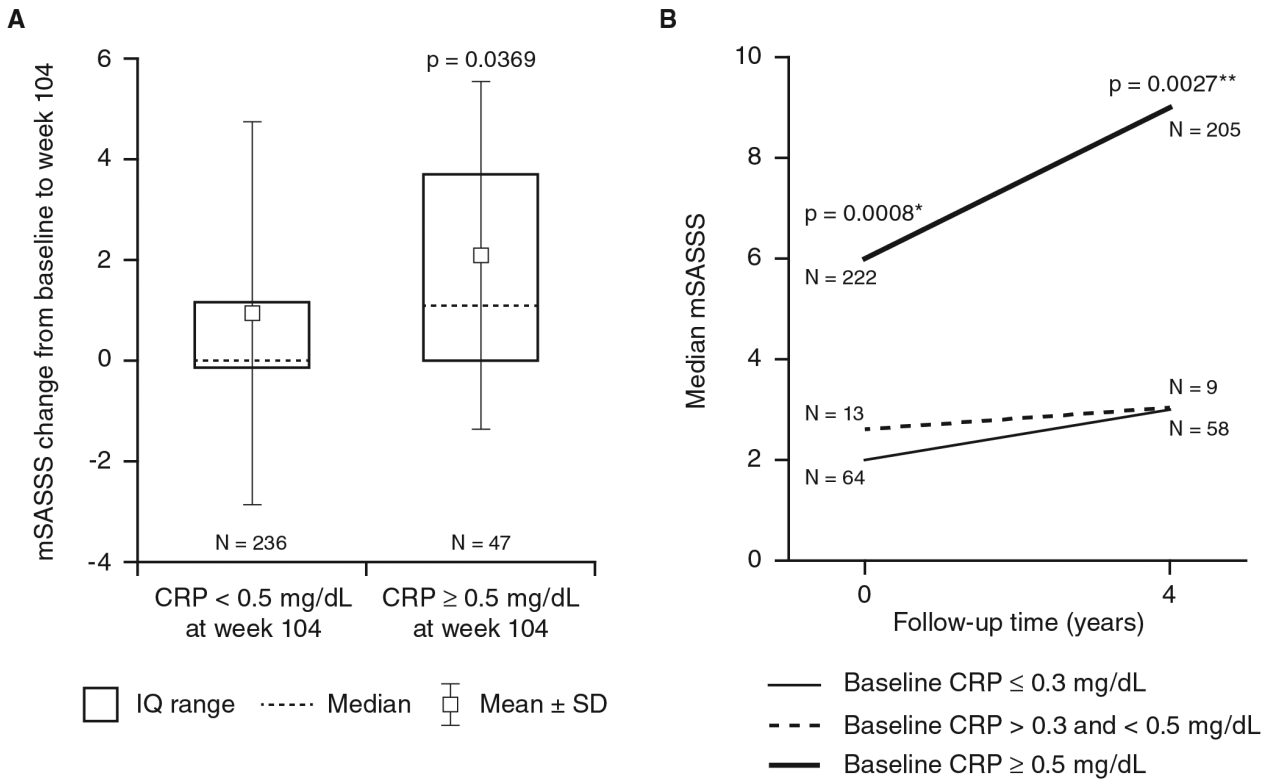
Timepoint	mSASSS Change < 2	mSASSS Change ≥ 2	p
Week 104			0.0014
n	219	71	
Week 0	1.0	1.7	0.0078
n	218	73	
Change from baseline to Week 14			0.0011
	–0.3	–0.9	
n	220	72	
Change from baseline to Week 24	–0.4	–1.0	
Week 208			0.0163
n	182	80	
Week 0	1.0	1.5	0.0423
n	183	82	
Change from baseline to Week 14			0.0019
	–0.4	–0.9	
n	182	83	
Change from baseline to Week 24	–0.4	–0.9	

CRP: C-reactive protein; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

indicated an increased risk of syndesmophyte formation at weeks 104 and/or 208 to be associated with baseline mSASSS, age, sex, and greater short-term decreases in serum CRP levels from baseline to Week 14 and Week 24. Elevated CRP levels at Week 14 or 24 were not significantly associated with subsequent new syndesmophyte formation. In this respect, our results are similar to a smaller study in patients with axSpA beginning anti-TNF therapy, in which larger, short-term decreases in, and normalization of, CRP levels were associated with development of new syndesmophytes and progression in mSASSS[15]. On the other hand, in terms of radiographic progression at weeks 104 and 208, only baseline mSASSS was a significant predictor of subsequent increase in mSASSS by ≥ 2 units.

Overall, these findings are consistent with the assumption that, despite the robust reduction of serum CRP levels in anti-TNF–treated patients, there can remain inflammation that appears to contribute to new bone formation. Residual inflammation in anti-TNF–treated patients has also been reported for other studies. In the ESTHER trial, for example, only 15% of patients treated with ETN achieved clinical remission accompanied by no spinal inflammation at 1 year[23]. Our findings are also consistent with data from the OASIS study[24], the certolizumab axSpA trial[25], and the treat-to-target recommendations for AS[26].

Based on the AS imaging data available in the literature, it is likely that spinal inflammation precedes bone formation in AS[4]. However, this sequence does not seem to be the only germane one, because the regression of inflammation induced by TNF antagonists, as shown by clinical signs and symp-



* p-value is to test mSASSS at baseline between CRP ≥ 0.5 and CRP ≤ 0.3 at baseline
** p-value is to test mSASSS at 4th year between CRP ≥ 0.5 and CRP ≤ 0.3 at baseline

Figure 2. Relationships between mSASSS and serum CRP levels, including mSASSS changes by CRP levels at (A) Week 104 and (B) median mSASSS over time. CRP: C-reactive protein; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; IQ range: interquartile range.

Table 3. Patients with mSASSS progression by CRP level, mg/dl, at Week 104. Values are n/N (%) unless otherwise specified.

Progression	CRP ≤ 0.3	CRP > 0.3	p
mSASSS change ≥ 2 from baseline to Week 104	52/222 (23.4)	21/61 (34.4)	0.0819
mSASSS change ≥ 2 from Week 104 to Week 208	44/214 (20.6)	13/54 (24.1)	0.5729
	CRP < 0.5	CRP ≥ 0.5	p
mSASSS change ≥ 2 from baseline to Week 104	54/236 (22.9)	19/47 (40.4)	0.0121
mSASSS change ≥ 2 from Week 104 to Week 208	46/226 (20.4)	11/42 (26.2)	0.3960

CRP: C-reactive protein; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

toms, MRI, and biomarkers, alone does not appear to be strong enough to inhibit radiographic progression in the first years of treatment[5,6,7]. The 2 MRI signals that have been shown to be associated with new bone formation are bone marrow edema (BME) and fat[4,27,28,29,30,31]. While the former likely represents osteitis, it remains unclear what the latter represents because granulation tissue is usually reported in these areas[32]. In any case, the most probable sequence of events in this scenario is that the initial inflammation, which may be induced by mechanical stress on a genetic background[33], at least in some cases followed by erosion[2], is then transformed into a tissue that is both inflammatory and degenerative, with the MRI signal demonstrating both BME and fat. From this tissue, syndesmophytes are more likely to develop than from any other MRI signal[27,28]. Importantly, at this stage in the disease process, anti-TNF therapies are not effective — showing why it appears to take years until the effect of anti-TNF therapy on bone formation becomes measurable[8,9].

A limitation of our study is the relatively small sample size. However, serial measurements within the same patients were available in our study while not available in others[11,22]. Additionally, given the length of time it appears to take for anti-TNF treatment to influence radiographic progres-

Table 4. Logistic regression analysis of syndesmophyte formation/radiographic progression adjusted by serum CRP levels and other patient and disease factors.

Variables	Syndesmophyte Formation*			
	Week 104		Week 208	
	OR (95% CI)	p	OR (95% CI)	p
CRP at baseline, n = 290				
Age, yrs	1.032 (1.004–1.061)	**0.0227**	1.035 (1.008–1.063)	**0.0116**
CRP at baseline	1.116 (0.977–1.275)	0.1072	1.155 (1.011–1.319)	**0.0338**
Disease duration, yrs	0.989 (0.954–1.026)	0.5471	0.998 (0.964–1.034)	0.9180
Male/female = 1/0	0.541 (0.289–1.012)	0.0544	0.544 (0.299–0.988)	**0.0454**
HLA-B27, positive/negative = 1/0	0.967 (0.443–2.114)	0.9337	0.973 (0.457–2.071)	0.9436
mSASSS at baseline	1.045 (1.026–1.064)	**< 0.0001**	1.031 (1.013–1.049)	**0.0006**
Smoking status, yes/no = 1/0	0.643 (0.374–1.105)	0.1099	0.598 (0.356–1.005)	0.0523
CRP at Week 14, n = 291				
Age, yrs	1.026 (0.998–1.054)	0.0641	1.031 (1.004–1.059)	**0.0246**
CRP at Week 14	0.989 (0.776–1.261)	0.9292	1.105 (0.885–1.378)	0.3774
Disease duration, yrs	0.987 (0.951–1.023)	0.4702	0.992 (0.958–1.028)	0.6722
Male/female = 1/0	0.554 (0.295–1.038)	0.0653	0.563 (0.310–1.023)	0.0592
HLA-B27, positive/negative = 1/0	1.002 (0.458–2.189)	0.9967	0.862 (0.403–1.843)	0.7012
mSASSS at baseline	1.054 (1.034–1.074)	**< 0.0001**	1.039 (1.021–1.058)	**< 0.0001**
Smoking status, yes/no = 1/0	0.598 (0.346–1.031)	0.0644	0.573 (0.340–0.966)	**0.0365**
CRP at Week 24, n = 292				
Age, yrs	1.027 (1.000–1.056)	0.0503	1.031 (1.004–1.059)	**0.0224**
CRP at Week 24	0.951 (0.749–1.208)	0.6818	0.976 (0.776–1.229)	0.8387
Disease duration, yrs	0.984 (0.949–1.021)	0.3934	0.992 (0.959–1.027)	0.6657
Male/female = 1/0	0.495 (0.262–0.936)	**0.0304**	0.543 (0.299–0.986)	**0.0448**
HLA-B27, positive/negative = 1/0	0.912 (0.416–2.003)	0.8193	1.020 (0.483–2.156)	0.9584
mSASSS at baseline	1.051 (1.031–1.070)	**< 0.0001**	1.037 (1.019–1.054)	**< 0.0001**
Smoking status, yes/no = 1/0	0.673 (0.392–1.158)	0.1525	0.605 (0.361–1.014)	0.0566
CRP change at Week 14, n = 291				
Age, yrs	1.030 (1.002–1.059)	**0.0375**	1.033 (1.006–1.061)	**0.0171**
CRP change at Week 14	0.836 (0.719–0.971)	**0.0190**	0.839 (0.724–0.972)	**0.0190**
Disease duration, yrs	0.993 (0.957–1.031)	0.7160	0.999 (0.964–1.035)	0.9478
Male/female = 1/0	0.557 (0.294–1.054)	0.0720	0.570 (0.311–1.044)	0.0687
HLA-B27, positive/negative = 1/0	1.002 (0.454–2.211)	0.9968	0.883 (0.410–1.902)	0.7513
mSASSS at baseline	1.051 (1.031–1.071)	**< 0.0001**	1.037 (1.019–1.056)	**< 0.0001**
Smoking status, yes/no = 1/0	0.599 (0.345–1.040)	0.0688	0.579 (0.342–0.980)	**0.0419**
CRP change at Week 24, n= 292				
Age, yrs	1.032 (1.004–1.061)	**0.0239**	1.036 (1.009–1.065)	**0.0092**
CRP change at Week 24	0.843 (0.733–0.969)	**0.0162**	0.828 (0.721–0.950)	**0.0073**
Disease duration, yrs	0.991 (0.955–1.028)	0.6220	1.000 (0.965–1.035)	0.9879
Male/female = 1/0	0.497 (0.261–0.946)	**0.0331**	0.543 (0.296–0.996)	**0.0486**
HLA-B27, positive/negative = 1/0	0.910 (0.411–2.013)	0.8156	1.039 (0.487–2.214)	0.9218
mSASSS at baseline	1.046 (1.027–1.066)	**< 0.0001**	1.032 (1.014–1.050)	**0.0003**
Smoking status, yes/no = 1/0	0.658 (0.381–1.137)	0.1339	0.585 (0.347–0.987)	**0.0446**

Variables	Radiographic Progression**			
	Week 104		Week 208	
	OR (95% CI)	p	OR (95% CI)	p
CRP at baseline, n = 262				
Age, yrs	1.014 (0.985–1.043)	0.3636	1.011 (0.983–1.040)	0.4430
CRP at baseline	1.094 (0.955–1.253)	0.1942	1.059 (0.926–1.212)	0.3998
Disease duration, yrs	0.983 (0.944–1.023)	0.4029	0.997 (0.960–1.036)	0.8827
Male/female = 1/0	0.509 (0.241–1.076)	0.0771	0.601 (0.291–1.242)	0.1693
HLA-B27, positive/negative = 1/0	0.814 (0.337–1.963)	0.6460	1.252 (0.542–2.893)	0.5986
mSASSS at baseline	1.037 (1.019–1.054)	**< 0.0001**	1.030 (1.012–1.047)	**0.0008**
Smoking status, yes/no = 1/0	0.974 (0.539–1.759)	0.9302	0.893 (0.506–1.577)	0.6965
CRP at Week 14, n = 265				
Age, yrs	1.010 (0.982–1.039)	0.4960	1.008 (0.981–1.037)	0.5524
CRP at Week 14	0.976 (0.759–1.254)	0.8489	1.003 (0.793–1.269)	0.9809
Disease duration, yrs	0.983 (0.945–1.023)	0.4070	0.992 (0.955–1.031)	0.6918
Male/female = 1/0	0.531 (0.255–1.102)	0.0893	0.665 (0.326–1.357)	0.2626
HLA-B27, positive/negative = 1/0	0.838 (0.349–2.014)	0.6929	1.283 (0.556–2.961)	0.5589
mSASSS at baseline	1.041 (1.023–1.059)	**< 0.0001**	1.033 (1.016–1.051)	**0.0001**
Smoking status, yes/no = 1/0	0.977 (0.544–1.755)	0.9379	0.823 (0.467–1.451)	0.5011

Table 4. Continued.

Variables	Radiographic Progression**			
	Week 104		Week 208	
	OR (95% CI)	p	OR (95% CI)	p
CRP at Week 24, n = 265				
Age, yrs	1.011 (0.983–1.040)	0.4364	1.009 (0.982–1.038)	0.5095
CRP at Week 24	1.024 (0.805–1.303)	0.8468	0.886 (0.682–1.153)	0.3678
Disease duration, yrs	0.979 (0.941–1.018)	0.2846	0.997 (0.961–1.035)	0.8743
Male/female = 1/0	0.559 (0.270–1.158)	0.1176	0.627 (0.307–1.281)	0.2003
HLA-B27, positive/negative = 1/0	0.828 (0.345–1.985)	0.6722	1.258 (0.547–2.896)	0.5892
mSASSS at baseline	1.038 (1.021–1.056)	**< 0.0001**	1.034 (1.017–1.051)	**0.0001**
Smoking status, yes/no = 1/0	1.006 (0.561–1.803)	0.9852	0.840 (0.478–1.479)	0.5464
CRP change at Week 14, n = 265				
Age, yrs	1.013 (0.984–1.042)	0.3860	1.011 (0.983–1.039)	0.4563
CRP change at Week 14	0.862 (0.745–0.997)	**0.0451**	0.898 (0.778–1.037)	0.1425
Disease duration, yrs	0.990 (0.951–1.031)	0.6187	0.996 (0.959–1.035)	0.8564
Male/female = 1/0	0.530 (0.253–1.110)	0.0923	0.656 (0.320–1.345)	0.2499
HLA-B27, positive/negative = 1/0	0.825 (0.340–1.999)	0.6695	1.251 (0.540–2.898)	0.6016
mSASSS at baseline	1.038 (1.020–1.056)	**< 0.0001**	1.031 (1.014–1.049)	**0.0003**
Smoking status, yes/no = 1/0	0.970 (0.537–1.752)	0.9185	0.829 (0.469–1.466)	0.5191
CRP change at Week 24, n = 265				
Age, yrs	1.014 (0.985–1.044)	0.3401	1.014 (0.986–1.042)	0.3452
CRP change at Week 24	0.898 (0.780–1.034)	0.1338	0.865 (0.753–0.993)	**0.0394**
Disease duration, yrs	0.984 (0.946–1.025)	0.4426	1.003 (0.966–1.042)	0.8811
Male/female = 1/0	0.560 (0.269–1.167)	0.1217	0.616 (0.299–1.267)	0.1882
HLA-B27, positive/negative = 1/0	0.847 (0.353–2.032)	0.7104	1.202 (0.522–2.769)	0.6661
mSASSS at baseline	1.036 (1.019–1.053)	**< 0.0001**	1.030 (1.013–1.047)	**0.0006**
Smoking status, yes/no = 1/0	0.980 (0.545–1.762)	0.9467	0.846 (0.479–1.495)	0.5653

* Syndesmophyte formation was defined as having ≥ 1 vertebral level on radiograph that changed from a score < 2 at baseline to an mSASSS of 2 or 3 at Week 104 or 208 according to at least 1 reader. ** Radiographic progression was defined as a change of ≥ 2 units in mSASSS from baseline to Week 104 or 208. Significant data are in bold face. CRP: C-reactive protein; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

Table 5. Spearman correlation analysis of serum CRP mg/dl levels and ASspiMRI-a scores.

ASspiMRI-a Timepoint	CRP Timepoint	No. Patients	Spearman Correlation Coefficient	p*
Baseline score	CRP at baseline	**89**	**0.36**	**0.0085**
Week 14				
Score	CRP at baseline	85	0.11	1.000
	CRP at Week 14	**85**	**0.33**	**0.0357**
	CRP change at Week 14	85	0.18	1.000
Change from baseline	CRP at baseline	**80**	**–0.33**	**0.0464**
	CRP at Week 14	79	0.31	0.1024
	CRP change at Week 14	**79**	**0.54**	**< 0.0001**
Week 104				
Score	CRP at baseline	68	0.07	1.000
	CRP at Week 14	68	0.13	1.000
	CRP change at Week 14	68	–0.01	1.000
	CRP at Week 104	67	0.01	1.000
	CRP change at Week 104	67	–0.02	1.000
Change from baseline	CRP at baseline	**66**	**–0.40**	**0.0177**
	CRP at Week 14	65	–0.15	1.000
	CRP change at Week 14	65	0.31	0.1914
	CRP at Week 104	65	–0.10	1.000
	CRP change at Week 104	**65**	**0.37**	**0.0452**

* Adjusted for multiplicity of testing through the Bonferroni method. Significant data are in bold face. CRP: C-reactive protein; ASspiMRI-a: ankylosing spondylitis spine magnetic resonance imaging activity.

sion/bone formation, evaluations of biomarkers and images beyond 4 years should be performed in future clinical trials. Of note, we did not perform dose-response analyses in our posthoc study because no difference in mSASSS change was observed between GOL 50 mg and 100 mg in a previous analysis of GO-RAISE radiographic data[9].

Results presented herein suggest that incomplete suppression of inflammation in patients with AS may be a relevant factor for new bone formation. Additionally, serum CRP appears to be a pertinent predictive biomarker for longterm AS progression among patients receiving TNF antagonists.

ACKNOWLEDGMENT

The authors thank the patients, the investigators, and the study personnel who made this trial possible. The authors also thank Michelle Perate, MS, and Mary Whitman, PhD, of Janssen Scientific Affairs LLC, medical writers who helped draft, collate author comments for, collect approvals for, and submit the manuscript.

REFERENCES

1. Baraliakos X, Braun J. Biologic therapies for spondyloarthritis: what is new? Curr Rheumatol Rep 2012;14:422-7.
2. Braun J, Baraliakos X, Golder W, Brandt J, Rudwaleit M, Listing J, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum 2003;48:1126-36.
3. Braun J, Baraliakos X, Hermann KG, van der Heijde D, Inman RD, Deodhar AA, et al. Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo- controlled GO-RAISE study. Ann Rheum Dis 2012;71:878-84.
4. Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819-25.
5. van der Heijde D, Landewé R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324–31.
6. van der Heijde D, Landewé R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063–70.
7. van der Heijde D, Salonen D, Weissman BN, Landewé R, Maksymowych WP, Kupper H, et al; Canadian (M03-606) study group; ATLAS study group. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009;11:R127.
8. Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M, Sieper J, et al. Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF-alpha antibody infliximab. Rheumatology 2007;46:1450–3.
9. Braun J, Baraliakos X, Hermann KG, Deodhar A, van der Heijde D, Inman R, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Ann Rheum Dis 2014;73:1107-13.
10. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645–54.
11. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:1369-74.
12. Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012;64:1388-98.
13. Visvanathan S, Wagner C, Marini JC, Baker D, Gathany T, Han J, et al. Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. Ann Rheum Dis 2008;67:511-7.
14. Pedersen SJ, Sørensen IJ, Garnero P, Johansen JS, Madsen OR, Tvede N, et al. ASDAS, BASDAI and different treatment responses and their relation to biomarkers of inflammation, cartilage and bone turnover in patients with axial spondyloarthritis treated with TNFα inhibitors. Ann Rheum Dis 2011;70:1375-81.
15. Pedersen SJ, Sørensen IJ, Lambert RG, Hermann KG, Garnero P, Johansen JS, et al. Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondyloarthritis treated with tumor necrosis factor inhibitors. Arthritis Rheum 2011;63:3789-800.
16. Inman RD, Davis JC Jr, Heijde Dv, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58:3402–12.
17. Braun J, Deodhar A, Inman RD, van der Heijde D, Mack M, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. Ann Rheum Dis 2012;71:661-7.
18. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
19. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
20. Deodhar A, Braun J, Inman RD, van der Heijde D, Zhou Y, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. Ann Rheum Dis 2015;74:757-61.
21. Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127–9.
22. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60:717-27.
23. Song IH, Hermann KG, Haibel H, Althoff CE, Poddubnyy D, Listing J, et al. Prevention of new osteitis on magnetic resonance imaging in patients with early axial spondyloarthritis during 3 years of continuous treatment with etanercept: data of the ESTHER trial. Rheumatology 2015;54:257-61.
24. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis 2014;73:1455-61.
25. van der Heijde D, Maksymowych WP, Landewé R, Stach C, Hoepken B, Davies O, et al. Factors associated with structural damage in the spine, as measured by x-ray, in patients with axial

spondyloarthritis treated with certolizumab pegol over 96 weeks. Ann Rheum Dis 2015;74 Suppl 2:268.
26. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis 2014;73:6-16.
27. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther 2008;10:R104.
28. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowych WP. Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. Arthritis Rheum 2011;63:2215-25.
29. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93–102.
30. Rudwaleit M, Jurik AG, Hermann KG, Landewé R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009;68:1520-7.
31. van der Heijde D, Machado P, Braun J, Hermann KG, Baraliakos X, Hsu B, et al. MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis. Ann Rheum Dis 2012; 71:369-73.
32. Appel H, Loddenkemper C, Grozdanovic Z, Ebhardt H, Dreimann M, Hempfing A, et al. Correlation of histopathological findings and magnetic resonance imaging in the spine of patients with ankylosing spondylitis. Arthritis Res Ther 2006;8:R143.
33. Edwards JC, Bowness P, Archer JR. Jekyll and Hyde: the transformation of HLA-B27. Immunol Today 2000;21:256-60.

APPENDIX 1. The following institutional review boards/ethics committees reviewed and approved this study: China Medical University Hospital Instituted Review of Board 9F, Taichung, Taiwan; Comité de Protection des Personnes Ile-de-France III, Hôpital Tarnier-Cochin 89, Paris, France; Commissie Medische ethiek van de Universitaire Ziekenhuizen KU Leuven/U.Z. Gasthuisberg, Leuven, Belgium; Ethikkommission der ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der WWU Münster, Münster, Germany; Human Experiment and Ethics Committee, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; HUS Helsingin ja Uudenmaan sairaanhoitopiiri, Medisiininen eettinen toimikunta, Biomedicum Helsinki, Finland; Institution Review Board, Biomedical Research Institute, Seoul National University Hospital, Jongro-gu, Seoul, South Korea; Institution Review Board, Dong-A University Hospital Clinical Research Center, Seo-Gu, Busan, South Korea; Institutional Review Board, Guro Hospital, Korea University Medical Center, Guro-Gu, Seoul, South Korea; Institution Review Board, Hanyang University Hospital, Sungdong-Ku, Seoul, South Korea; Institution Review Board, Pusan National University Hospital, Seo-Gu, Busan, South Korea; Institutional Review Board, Seoul St. Mary's Hospital/The Catholic University of Korea, Seocho-gu, Seoul, South Korea; Joint Institution Review Board No. 201, Taipei, Taiwan; METC azM/UM Maastricht, Maastricht, the Netherlands; and Western Institutional Review Board, Olympia, Washington, USA.