

# Correspondence



## INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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## Extremity Magnetic Resonance Imaging

To the Editor:

In the October 2006 issue of *The Journal*, an editorial by Dr. J.T. Sharp discussed the issue of magnetic resonance imaging (MRI) using a low-field 0.2 Tesla (T) scanner versus a standard whole-body 1.5 T scanner for imaging rheumatoid arthritis (RA)<sup>1</sup>.

Dr. Sharp acknowledges the significant benefits of a low-field extremity machine over large-bore, whole-body magnets including lower purchase, installation and maintenance costs, the ability to install the machine in a smaller clinical center because such machines do not require extensive shielding, and the ease with which patients can be placed inside the device for imaging without the concern of claustrophobia. We agree with all these benefits of using an extremity MRI machine and have also acknowledged the benefits in a recent publication<sup>2</sup>. Dr. Sharp also notes the significant weaknesses of low-field MR scanners, the primary one being the compromise in image quality. The low-field scanner that Dr. Sharp refers to in his criticism is a 0.2 T scanner, images of which are shown in Dr. T.S. Chen's article in the same issue<sup>3</sup>.

The "tradeoff" of image quality versus cost and convenience of an extremity scanner is certainly a concern and raises issues such as those addressed by Sharp. However, it is important to recognize that other extremity MRI machines exist in which image quality is not sacrificed. For instance, ONI Medical Systems Inc. (Wilmington, MA, USA) manufactures a higher-field 1.0 T extremity scanner (OrthOne™) that affords the same advantages as those of the 0.2 T machine but without the disadvantage of poor image quality. For instance, this scanner can also be sited in a clinical office, affording easy access to patients and clinicians and offering patients a quiet, comfortable and convenient experience. This scanner is simple to operate and offers robust pulse sequences for contrast-enhanced studies, late-echo imaging and expanded-volume fat-suppressed visualization. The manufacturers of the 1.0 T machine report that the return on investment is typically less than 2 patients per day compared to 6–8 patients per day required to support a whole-body scanner<sup>4</sup>.

The OrthOne™ extremity scanner has been used for research purposes in the investigation of knee osteoarthritis<sup>2,5,6</sup>. Our group has recently reported that knee cartilage morphometry can be quantified with precision similar to that achieved using a 1.5 T system<sup>2</sup>. While these studies have focused upon imaging of the knee joint, extremity scanners are also capable of imaging the hand, wrist, elbow, foot, and ankle. Images of a hand affected by RA acquired with our OrthOne™ system are shown in Figure 1: image quality is clearly superior to that obtained using a 0.2 T machine. In other words, the use of an extremity MR scanner such as the 1.0 T system discussed here does not inevitably equate to a loss of image quality. To the contrary, the existence of higher field dedicated extremity scanners affords advantages of economy and accessibility, while providing images of comparable quality to those obtained with larger whole-body clinical scanners operating at high-field strengths.

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Figure 1. Images of a hand affected by RA acquired with the OrthoOne system; image quality is superior to that obtained using a 0.2 T machine.

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imaging is more sensitive than radiographs in detecting change in size of erosions in rheumatoid arthritis. *J Rheumatol* 2006; 33:1957-67.

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## Dr. Sharp replies

To the Editor:

Beattie and colleagues have described their experience with a 1.0 Tesla (T) extremity magnetic resonance imaging (MRI) machine and quote articles by others. In my editorial I purposely did not review the experience with the 1.0 T machine. Experience with this machine is extremely limited and the issues of tradeoff with the more expensive, standard 1.5 T, or even more powerful equipment, are not yet well defined. Those with experience with the 1.0 T machine report that the image quality approaches that of a 1.5 T device. Further, as Beattie, *et al* note, short-tau inversion recovery (STIR) images can be obtained with the lower field equipment. This early experience is encouraging and may mean that sufficient quality of the images produced will make it possible for rheumatologists and orthopedists to take advantage of the greater comfort and convenience of an "office" MRI. However, the cost advantage when comparing 0.2 T versus 1.5 T to 1.0 T versus 1.5 T is greatly decreased, although not completely abolished. It should be noted that 1.0 T is said to be the highest power that can be used in a configuration that will accommodate inserting a single extremity.

Because the 1.0 T equipment has been marketed only recently, it is not clear that the ultimate cost of the machine can be predicted or, for that matter, whether there will be sufficient demand to sustain a market for this product. However, the current price is not attractive for the solo practitioner or small groups. It seems likely that only institutions that can use the 1.0 T machine as supplementary equipment to accommodate patients who have difficulty when imaged in the standard MRI machine, because of active arthritis, physical deformity, or claustrophobia, will find it attractive in the early stages of its availability. Only time will tell whether it will take 5, 10, or 20 or more physicians in a single group who have large numbers of patients who would benefit from the advantages of an extremity machine to make the instrument economically attractive.

Beattie and colleagues are to be commended for pioneering this effort, but it will take many more studies comparing the 1.0 T to the 1.5 T equipment to be able to accurately evaluate the difference in quality of image and whether image quality difference ever compromises information needed for decision-making and if so, how often. Even with the higher powered magnet in the new equipment the question is still, what are the tradeoffs and do any of them compromise patient care?

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## Levels of Evidence for Epidural Steroid Injections

To the Editor:

In the review of conservative treatments for mechanical neck disorders (MND) by Gross, *et al*<sup>1</sup>, there seems to be an inconsistency in the use of levels of evidence for epidural steroid injections. According to the authors'

Table 2, evidence from single low-quality trials should be graded as "limited." And low-quality trials were determined by scores of less than 3 on Jadad's scale and less than 6 on van Tulder's scale. For epidural steroid injections, the only trial that they found (Stav, *et al*<sup>2</sup>, their reference 48) had a trial method score of 2 on Jadad's scale and 3 on van Tulder's scale. In spite of this, the evidence for epidural steroid injections is graded as "Moderate" both in Table 4 and in the Results section. Consequently, we think that the level of evidence should be changed to "Limited" for epidural steroid injections. In addition, we are concerned that the Conclusion in the abstract states that intramuscular lidocaine injections are effective for chronic MND, when the conclusion is based upon a single trial<sup>3</sup> with a poor trial method score of 1 on the Jadad scale and 2 on the van Tulder scale.

In our opinion, the possible beneficial effects of these 2 injection therapies remain uncertain, and the review seems to have overrated their value.

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## Gross, *et al* reply

To the Editor:

We thank Bjordal and Joensen for their thorough review of our recently published systematic review. We agree that we have overclassified the study by Stav, *et al*. Bjordal and Joensen's comments are consistent with our focused medicines and injections systematic review<sup>1</sup>, in which we classified the Stav trial as providing limited evidence. Bjordal and Joensen are correct that the trial reported by Esenyel, *et al*<sup>2</sup> was classified as limited evidence. However, we considered these results with other evidence from our Cochrane Review<sup>1</sup>, where intramuscular injection of lidocaine was superior to placebo and to dry needling<sup>2-4</sup>. To provide a consistent presentation across our reviews we chose to highlight particular findings in the abstract.

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### Efficacy and Safety of Etanercept in the Treatment of Scleroderma-Associated Joint Disease

To the Editor:

Joint pain and stiffness are common complaints in scleroderma and may represent a true inflammatory synovitis in a subset of patients<sup>1</sup>. Yet effective treatment remains problematic. We describe the efficacy and safety of etanercept in scleroderma patients with active joint disease.

We conducted a retrospective analysis of patients with scleroderma seen at the Johns Hopkins Scleroderma Center (JHSC) who had active joint disease and were treated with standard doses of etanercept (25 mg twice weekly or 50 mg once weekly). Patients studied either met American College of Rheumatology criteria for scleroderma<sup>2</sup> or had at least 3 of 5

features of the CREST syndrome (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias). Inflammatory joint involvement was defined by the detection of synovitis or inflammatory signs on examination, which were identified on chart review by the use of the terms "erythema," "edema," "warmth," "active joint disease," or "synovitis" in describing the joint examination. Demographic data, clinical characteristics of disease, duration of treatment with etanercept, and clinical outcome measures were recorded from the JHSC database and are summarized in Table 1. Primary efficacy outcome measures included a positive response at last followup visit if a significant decrease in synovitis was noted by the physician and if complete resolution of symptoms of joint pain was documented. The Health Assessment Questionnaire (HAQ) score was a secondary outcome measure. The Rodnan skin scores and pulmonary function test results were followed with therapy.

Eighteen patients were treated with etanercept for inflammatory joint involvement from December 1998 to May 2005, with duration of therapy ranging from 2 to 66 months (mean 30). All 18 patients were female, ranging in age from 25 to 71 years (mean 44). Three of 18 patients (17%) were positive for antiribonucleoprotein (RNP) antibodies; 8 of 17 patients (47%) were positive for rheumatoid factor (RF); and 3 of 12 (25%) were positive for antibodies to cyclic citrullinated peptides (CCP). Concomitant medications used during the course of etanercept treatment included nonsteroidal antiinflammatory drugs (18 patients), methotrexate (15 patients; doses ranging from 2.5 mg to 25 mg weekly, average dosage 12 mg), hydroxychloroquine (5 patients), prednisone (9 patients; doses ranging from 0.5 mg to 15 mg daily, average dosage 5 mg), and minocycline (2 patients).

Fifteen of 18 (83%) patients treated with etanercept had positive responses, with a significant decrease in signs of inflammation or synovitis on followup examination and complete resolution of joint symptoms. One patient was able to discontinue etanercept due to prolonged remission with inactive joints. Three patients (17%) had persistent signs of synovitis and/or joint symptoms, and they were considered nonresponders. These nonresponders were treated for an average of 14 months and had waxing and waning musculoskeletal findings during treatment. However, at the

Table 1. Patient characteristics and response to etanercept therapy. All patients here were female. Positive responses were those in which a dramatic decrease in signs of inflammation or synovitis was noted by the physician at followup and if resolution of patient symptoms of joint pain was documented.

Patient	Age, yrs	Race	SSc Subtype	ACA	RNP	Topo	RF	CCP	Duration of Treatment, mo	Positive Response to Treatment	Change in HAQ
1	48	C	Limited	-	+	-	-	-	66	Yes	0
2	42	AA	Diffuse	-	-	+	+	+	54	Yes	-0.6
3	60	C	Limited	+	-	-	-	-	55	Yes	+0.8
4	43	In	Limited	-	-	+	+	-	41	Yes	+0.6
5	53	C	Diffuse	-	-	-	ND	-	47	Yes	-0.3
6	60	C	Limited	-	-	-	-	-	51	Yes	+0.3
7	26	C	Diffuse	-	-	-	-	-	42	Yes	-0.3
8	56	C	Diffuse	-	+	-	+	-	23	Yes	+0.7
9	67	A	Diffuse	-	-	-	+	+	23	No	-1.6
10	50	C	Limited	-	-	-	+	+	53	Yes	-0.3
11	50	C	Limited	-	-	-	-	ND	15	No	-1.6
12	48	AA	Limited	-	+	-	+	ND	26	Yes	0
13	40	C	Diffuse	-	-	-	-	ND	5	No	ND
14	25	ME	Limited	-	-	-	-	-	12	Yes	0
15	43	C	Limited	-	-	+	-	-	9	Yes	-0.2
16	66	C	Limited	-	-	-	+	ND	9	Yes	-1.3
17	65	C	Limited	-	-	-	-	ND	2	Yes	ND
18	71	AA	Limited	-	-	+	+	ND	13	Yes	-0.2

C: Caucasian; AA: African American; In: Indian; A: Asian; ME: Middle Eastern; SSc: scleroderma; ACA: anticentromere antibody; RNP: antiribonucleoprotein antibody; topo: anti-topoisomerase antibody; RF: rheumatoid factor; CCP: anti-cyclic citrullinated peptide antibody; HAQ: Health Assessment Questionnaire; ND: not determined/ no sample available.

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time of latest followup, their responses were deemed not significantly improved. No association was noted between RF, CCP, or RNP status with response to etanercept.

Mean HAQ scores from baseline to latest available followup decreased from  $1.08 \pm 0.70$  to  $0.74 \pm 0.56$  ( $p = 0.13$ ). The mean skin score decreased during therapy from  $6.63 \pm 6.35$  to  $3.94 \pm 2.38$  ( $p = 0.12$ ).

A slight decline in pulmonary function was observed in the cohort as a whole during treatment with etanercept. The mean percentage predicted DLCO of the cohort decreased 5.1 percentage points (95% confidence interval  $-10.4$  to  $+0.18$ ), and the mean percentage predicted FVC decreased by 1.4 percentage points (95% CI  $-5.8$  to  $+2.9$ ). Both these decreases were not statistically significant, and when a case-control comparison was done with a group of patients who were not treated with etanercept or another tumor necrosis factor (TNF) antagonist ( $n = 36$ ), a similar decline was seen (data not shown). These data suggest that the changes observed likely reflect the natural decline that can occur in a population of patients with scleroderma and that etanercept therapy does not appear to have any clinically appreciable effect on lung function in these patients.

There were no reported incidents of opportunistic infections, anaphylaxis, hospitalizations, or death attributed to etanercept therapy. Etanercept was discontinued in one patient after development of a lupus-like reaction (as reported<sup>3</sup>). In a second patient, etanercept was discontinued after a marked decline in lung function was observed.

Our case series demonstrates that etanercept appeared to be efficacious in improving active inflammatory joint disease in a subset of scleroderma patients, and it was generally safe and well tolerated. Mean HAQ scores also decreased with therapy, paralleling the improvement in joint disease. Etanercept did not appear to worsen scleroderma skin disease, as the cohort's mean modified Rodnan skin score declined, despite some concerns that TNF antagonists may worsen fibrosis associated with scleroderma by allowing increased production of profibrotic cytokines by transforming growth factor- $\beta$ <sup>4</sup>. Prospective, randomized, blinded controlled trials are warranted to further define the role of etanercept or other TNF antagonists in the treatment of scleroderma-associated joint disease.

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We thank April Thurman for technical support; Pamela Hill for editorial assistance; and the Scleroderma Research Foundation for its support of the JHSC.

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## Association of Interleukin 18 Polymorphisms with Adult Onset Still's Disease in Korea

To the Editor:

Adult onset Still's disease (AOSD) is a multisystemic inflammatory disorder of unknown origin. The pathogenesis of AOSD is associated with elevated levels of serum cytokines such as interleukin 1 (IL-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6, IL-18, and interferon- $\gamma$  (IFN- $\gamma$ ). A recent study showed that levels of serum IL-18 in patients with active AOSD were very high and were correlated with the disease severity and activity<sup>2</sup>. IL-18 is a new member of the IL-1 family, and it is a potent inducer of IFN- $\gamma$  from T cells and natural killer cells, promoting a Th-1-type immune response through the activation of nuclear factor- $\kappa$ B<sup>3</sup>. In Japanese studies, IL-18 single-nucleotide polymorphisms (SNP) in the promoter region have been associated with juvenile idiopathic arthritis (JIA)<sup>4</sup> and AOSD<sup>5</sup>. We hypothesized that SNP of the IL-18 gene might be associated with AOSD in Koreans.

We genotyped 4 SNP of the IL-18 gene, denoted  $-656G/T$ ,  $-607C/A$ ,  $-137G/C$ , and  $1248A/G$ , in 79 patients with AOSD and 130 healthy Korean individuals. All AOSD patients satisfied the criteria of Yamaguchi, *et al*<sup>6</sup>. Written informed consent was obtained from all participants before enrollment.

Patients were subdivided into groups according to disease course: monocyclic systemic, polycyclic systemic, or chronic articular type<sup>7</sup>. Genotyping was performed using the sequence-specific polymerase chain reaction method. Allelic, genotypic, and haplotypic associations were analyzed by chi-square test. The frequencies of the haplotype and linkage disequilibrium were estimated using the Arlequin program (available from: <http://anthro.unige.ch/software/arlequin/about.php>).

No differences in genotypic frequencies were found between patients and the controls. The A allele at position  $-607$  was more frequent in AOSD patients than in controls (OR 1.510, 95% CI 1.01–2.25,  $p = 0.042$ ; Table 1). The AA genotype at position  $-607$  was more frequent in patients with the monocyclic systemic type disease than in controls (OR 3.538, 95% CI 1.17–10.70,  $p = 0.031$ ; Table 2).

SNP at positions  $-137$  and  $-607$  have been suggested to have an influence on IL-18 gene activity, as both SNP alter the transcription factor binding site. In the previous study, patients homozygous for C at position  $-607$  and G at position  $-137$  had increased promoter activity and higher levels of IL-18 mRNA expression compared to other genotypes<sup>8</sup>. We found that the A allele was associated with AOSD patients, and the AA genotype at position  $-607$  specifically with the monocyclic systemic disease type. When we excluded the monocyclic systemic type, there was no difference between the AOSD patients and controls in the allelic and genotypic frequencies at position  $-607$ . Sugiura, *et al*<sup>4,5</sup> showed that 12 SNP within the promoter region of the IL-18 gene were associated with susceptibility to JIA in Japanese patients. There was a strong association between the diplotype configuration of S01/S01 of the IL-18 gene and JIA as well as AOSD. T at position  $-656$ , A at position  $-607$ , and G at position  $-137$  were the components of haplotype S01. The diplotype configuration of S01/S01 was linked to significantly higher serum levels of IL-18 in systemic JIA. In addition, the serum level of IL-18 was reported to be higher in patients with the monocyclic systemic disease than in those with the chronic articular type<sup>7</sup>. These data suggest that the A allele in  $-607$  may be associated with higher levels of serum IL-18, and with the monocyclic systemic disease rather than the other subtypes. When we reconstructed the 4 main haplotypes in this study — GCGA, TAGA, TACG, and TCGA — we found no differences in haplotype frequencies between patients and controls, but there was strong linkage disequilibrium in all 4 SNP (all  $D > 0.6$ ,  $p < 0.0001$ ). Also, the frequency of the TAGA/TAGA diplotype configuration was not different between the AOSD patients and the controls (OR 2.149, 95% CI 0.882–5.238,  $p = 0.087$ ). When we measured the IL-18 concentrations from culture supernatants of mononuclear cells in the presence of PMA-ionomycin, the mean IL-18 level in the controls carrying the TAGA/TAGA diplotype did not differ from that in controls carrying the GCGA/GCGA diplotype (data not shown).

Table 1. Allelic and genotypic frequencies of IL-18 gene polymorphisms in Korean patients with AOSD and controls.

Locus		AOSD, n (%)	Control, n (%)	p	OR (95% CI)	
Allele	-656	G	80 (50.6)	139 (53.5)	0.574	0.893 (0.60–1.32)
		T	78 (49.4)	121 (46.5)		
	-607	A	78 (49.4)	102 (39.2)	0.042	1.501 (1.01–2.25)
		C	80 (50.6)	158 (60.8)		
	-137	G	145 (91.8)	231 (88.8)	0.335	0.714 (0.36–1.41)
		C	13 (8.2)	29 (11.2)		
1248	A	145 (91.8)	232 (89.2)	0.397	1.346 (0.68–2.68)	
	G	13 (8.2)	28 (10.8)			
Genotype	-656	GG	19 (24.1)	40 (30.8)	0.490	
		GT	42 (53.2)	59 (45.4)		
		TT	18 (22.8)	31 (23.8)		
	-607	AA	17 (21.5)	15 (11.5)	0.083	
		CA	44 (55.7)	72 (55.4)		
		CC	18 (22.8)	43 (33.1)		
	-137	GG	68 (86.1)	104 (80.0)	0.471	
		GC	9 (11.4)	23 (17.7)		
		CC	2 (2.5)	3 (2.93)		
	1248	AA	67 (84.8)	105 (80.8)	0.720	
		AG	11 (13.9)	22 (16.9)		
		GG	1 (1.3)	3 (2.3)		

Table 2. Genotypic frequencies of IL-18 single-nucleotide polymorphisms by disease course. The patients who had disease duration less than 1 year were excluded from the analysis of disease course. Monocyclic systemic type: only one episode of systemic manifestation, followed by a complete remission within 1 year after disease onset; polycyclic systemic type: > 1 episode of systemic manifestation, followed by partial or complete remission within 1 year after disease onset or subsequent attack; chronic articular type: persistent arthritis involving at least one joint area and lasting more than 6 months.

Locus	Genotype	AOSD, n (%)	Control, n (%)	p	OR (95% CI)
Monocyclic systemic type (n = 19)					
-656	TT	6 (31.6)	31 (23.8)	0.570	1.474 (0.57–4.20)
	GG + GT	13 (68.5)	99 (76.2)		
-607	AA	6 (31.6)	15 (11.5)	0.031	3.538 (1.17–10.70)
	CC + CA	13 (68.5)	115 (88.5)		
-137	CC	1 (5.3)	3 (2.3)	0.424	2.352 (0.23–23.84)
	GG + GC	18 (94.7)	127 (97.7)		
1248	GG	0 (0.0)	3 (2.3)	1.000	—
	AA + AG	19 (100.0)	127 (97.7)		
Polycyclic systemic type (n = 25)					
-656	TT	5 (20.0)	31 (23.8)	0.677	0.789 (0.27–2.30)
	GG + GT	20 (80.0)	99 (76.2)		
-607	AA	5 (20.0)	15 (11.5)	0.324	1.917 (0.62–5.86)
	CC + CA	20 (80.0)	115 (88.5)		
-137	CC	1 (4.0)	3 (2.3)	0.509	1.764 (0.17–17.67)
	GG + GC	24 (96.0)	127 (97.7)		
1248	GG	1 (4.0)	3 (2.3)	0.509	1.764 (0.17–17.67)
	AA + AG	24 (96.0)	127 (97.7)		
Chronic articular type (n = 24)					
-656	TT	4 (16.7)	31 (23.8)	0.441	0.639 (0.20–2.01)
	GG + GT	20 (83.3)	99 (76.2)		
-607	AA	3 (12.5)	15 (11.5)	1.000	1.095 (0.29–4.11)
	CC + CA	21 (87.5)	115 (88.5)		
-137	CC	0 (0.0)	3 (2.3)	1.000	—
	GG + GC	24 (100.0)	127 (97.7)		
1248	GG	0 (0.0)	3 (2.3)	1.000	—
	AA + AG	24 (100.0)	127 (97.7)		

It seemed that high levels of production of IL-18 might not be directly associated with the IL-18 gene polymorphisms tested in this study. The possible reasons for the inconsistency compared to other studies are unclear. One possible explanation for the discrepancy would be strong linkage disequilibrium in the 4 SNP of the IL-18 promoter region. We should consider that there might be other unknown functional mutations elsewhere in the IL-18 sequence, and also in the other independent genes affecting the secretion of IL-18. Another explanation might be the variation of genetic susceptibility between ethnic groups<sup>9</sup>. Allelic heterogeneity exists between ethnic groups, and different variations within the same gene should contribute to disease risk<sup>10</sup>.

Our study was on a relatively large scale considering the rarity of AOSD. We showed that the A allele at position -607 in the IL-18 promoter region may be associated with the development of AOSD, especially in the monocyclic systemic subgroup.

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## Correction

Geuskens GA, Burdorf A, Hazes JMW. Consequences of rheumatoid arthritis for performance of social roles — A literature review. *J Rheumatol* 2007;34:1248-60. In a source document for this literature review (Dadoniene J, Stropuviene S, Venalis A, Boonen A. High work disability rate among rheumatoid arthritis patients in Lithuania. *Arthritis Rheum* 2004;51:433-439), in Table 3, the difference in employment rate between patients with rheumatoid arthritis (RA) and the Lithuanian population was erroneously exchanged for data for men and women. As a consequence, odds ratios for not having a paid job for male and female RA patients were calculated incorrectly within the literature review.

For the study by Dadoniene, *et al*, the correct odds ratios for male and female patients with RA not to have a paid job were 4.64 and 1.92, respectively (absolute difference with population 36.6% and 16.1%, respectively). This finding is in agreement with a study conducted in The Netherlands (van Jaarsveld CH, Jacobs JW, Schrijvers AJ, van Albeda-Kuipers GA, Hofman DM, Bijlsma JW. Effects of rheumatoid arthritis on employment and social participation during the first years of disease in The Netherlands. *Br J Rheumatol* 1998;37:848-853). Therefore, the revised conclusion in both studies is that the influence of RA on not having a paid job was greater among men than among women. We regret the error.