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.

Letters should be submitted via our online submission system, available at the Manuscript Central website: http://mc.manuscriptcentral.com/jrheum For additional information, contact the Managing Editor, The Journal of Rheumatology, E-mail: jrheum@jrheum.com

Should Physicians Manipulate Their Assessment Tools? No, They Shouldn't!

To the Editor:

I read with great interest the article by El Miedany, *et al* regarding disease activity assessment in patients with rheumatoid arthritis (RA) receiving tumor necrosis factor (TNF)-blocker therapy[1].

Despite the fact that disease activity assessment is of particular importance to the rheumatologic community, I wonder how this paper successfully passed the review process of *The Journal*, particularly with respect to the statistical basis from which the conclusions are drawn.

The only well founded result is the positive correlation between disease activity score (DAS, including a 28-joint count DAS28) and the DAS28 C-reactive protein (DAS28-CRP) for groups of patients[2,3]. This already well-described correlation has no value, however, for monitoring a single patient as the respective DAS values may differ substantially in individuals due to discrepancies between erythrocyte sedimentation rate (ESR) and CRP.

All other results and subsequent conclusions are based on unjustified assumptions both from a statistical viewpoint and from the intentions of the originators of the DAS, as I understand them. I was under the impression that the DAS was developed to combine physician-dependent variables (joint counts), objective variables of inflammation, and a patient's self-assessment to express disease activity numerically[4].

It seems completely inappropriate to substitute the patient's global assessment (PGA) with the physician's global assessment (PhGA) giving it *a priori* the same weight within the formula. Additionally, the authors did no reliability testing or factor analysis of these new scores to gain insight into their psychometric properties.

Maintaining the primary bias, EULAR response criteria were also applied to the DAS variations without any validation[5]. Given that PhGA changed far more than PGA in this particular study, these new scores might have revealed more and better responses. Effect sizes, however, can be regarded only as surrogate measures of sensitivity to change, as the name indicates, and repeating a false procedure does not increase its validity.

We performed reliability testing and factor analysis of all 4 DAS variations proposed by the authors for one of our RA patient cohorts comprising 399 routine out-patients (307 women, 92 men, mean age 60.6 years; median DAS28 3.42 ± 1.5)[6]. We found that internal consistency, as expressed by standardized item alpha, was very similar for the 4 constructs, independent of the inclusion of ESR or CRP, PGA or PhGA (Table 1). Regardless of the DAS variation analyzed, the alpha was below the threshold of 0.70, which is regarded as a marker of substantial reliability. Even an alpha of 0.70 indicates that the standard error of measurement will be more than half (0.55) a standard deviation[7].

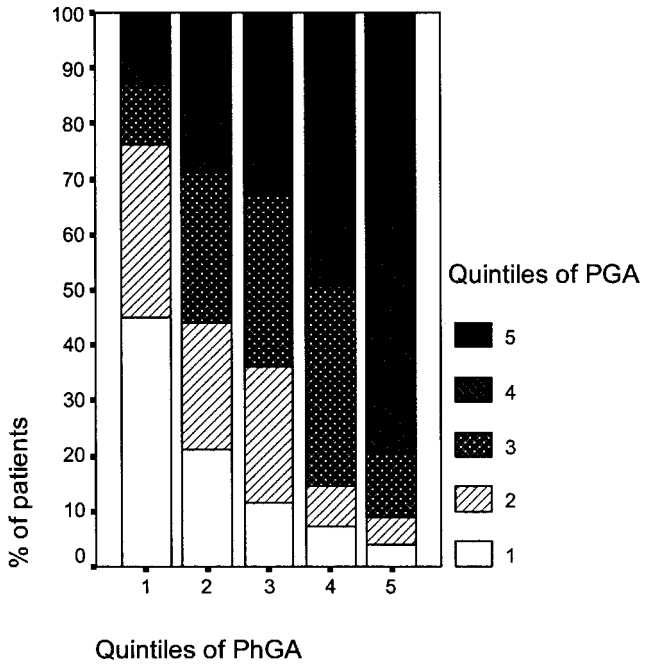

Figure 1. Crosstabs show the relationship between patient's (PGA) and physician's (PhGA) global assessment (kappa = 0.166; $p < 0.001$).

On principal component analysis, all DAS28 variations were one-dimensional with comparable item loadings (Table 2)[8]. We applied kappa statistics for assessment of the relationship between PhGA and PGA, by comparing quintiles of the respective visual analog scale (VAS) values in our 399 patients. We detected only a weak relationship as expressed by kappa of 0.166, although it reached statistical significance ($p < 0.001$) (Figure 1). This relates to the incongruence between patients' and physicians' perceptions of disease activity and its changes[9].

Despite problems with internal consistency the DAS28 was proven to be substantially well correlated with patients' satisfaction with disease stage[10]. Why, then, substitute a patient's opinions with the physician's assessment? It does not enhance the *a priori* weak internal consistency of the DAS and it does not exert any influence on dimensionality or item loading. However, it does exclude the target, namely the patient, from therapy assessment, and this may have an influence on compliance.

How long can you continue to explain to a patient that a treatment is successful when she/he does not feel the improvement? Was this study perhaps performed to increase the justification for expensive treatments?

I feel this paper is a substantial step away from individualized, patient oriented treatment that we urgently need to ameliorate our treatment results and thereby improve the quality of life of our patients. Enhanced treatment success will not be achieved by changing our assessment tools for our own purposes, but by optimizing our therapeutic measures in cooperation with our patients. To this end acknowledgment of and respect for their thoughts and wishes is mandatory.

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Table 1. Reliability test results for the 4 DAS constructs. N = 399.

	DAS28	DAS28-CRP	DAS28 incl. PhGA	DAS28-CRP incl. PhGA
Standardized item alpha	0.65	0.63	0.69	0.66

DAS: disease activity score; PhGA: physician's global assessment; CRP: C-reactive protein.

Table 2. Component matrices (item loading) for the 4 DAS constructs. Extraction method: principal component analysis, 1 component extracted. N = 399.

	DAS28	DAS28-CRP	DAS28 incl. PhGA	DAS28-CRP incl. PhGA
TJC	0.831	0.845	0.714	0.733
SJC	0.798	0.772	0.863	0.856
ESR	0.404	—	0.493	—
CRP	—	0.334	—	0.397
PGA	0.730	0.747	—	—
PhGA	—	—	0.786	0.781

DAS: disease activity score; TJC: tender joint count, SJC: swollen joint count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PGA: patient global assessment, PhGA: physician global assessment.

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Dr. El Miedany and Dr. El Gaafary reply

To the Editor:

We thank Dr. Leeb for his interest in our study[1] and are happy that our work has stimulated such comments. Perhaps this provides us with the opportunity to express some further thoughts on our suggested approach.

After reviewing both Dr. Leeb's letter regarding our study and his earlier study[2], we believe there is a major discrepancy that should be highlighted. Dr. Leeb based his reply on his study that included 399 patients with rheumatoid arthritis (RA), 29 of whom were receiving tumor necrosis factor (TNF) blockers and 370 of whom were receiving disease modifying antirheumatic drugs (DMARD). In contrast, all patients in our study were receiving TNF therapy. Perhaps such a difference in the distribution of therapeutic regimens in each study is the simplest justification for changing our assessment policy. As we noted in our introduction, disease activity score (DAS) was originally developed based on patients receiving DMARD therapy that usually takes between 3-6 months to show some effect. Since the introduction of TNF therapy, there has been a swift and significant change in the rate of improvement in disease activity associated with a trend toward induction of remission as early as possible. We believe that such a change in therapeutic tactics should be paralleled by a change in the way we monitor disease activity. Furthermore, such a major contrast between studies may simply explain the difference in the 2 outcomes.

Our aim was not focused on testing reliability of the new DAS. As we mentioned, our aim was to evaluate the DAS using various measures to determine the best instrument that indicates good response and also satisfies the demands of clinical rheumatology. Discrepancies between erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were taken into consideration in the new set of indicators (DAS2-4).

Table 1 displays item to total score correlation of the different DAS and can be regarded as a test of internal consistency. Effect size is a statistical representation of change over time in a measure that is standardized by dividing the change value by the standard deviation of its baseline values. Effect size can also be used to compare the sensitivity to change of various outcome measures[3].

In agreement with the literature and with Dr. Leeb, DAS was developed to assess disease activity. Keeping this in mind, we carried out our study to determine the best variables to monitor disease activity. As we wrote in our Discussion, we did not recommend omitting patient variables such as patient global assessment (PGA), pain score, or the health assessment questionnaire (HAQ). We suggested keeping a record of all these factors. However, when it comes to assessing disease activity and monitoring drug therapy, we need to include the best variables: this explains why we suggested using physician global assessment (PhGA) and CRP.

Table 1. Item to total correlation of the different disease activity scores (DAS) before and after 6 months of therapy.

	DAS I	DAS II	DAS III	DAS IV
TJC				
Baseline	0.860**	0.895**	0.847**	0.860**
After 6 mo	0.534**	0.472**	0.618*	0.539**
SJC				
Baseline	0.690**	0.713**	0.744**	0.691**
After 6 mo	0.620*	0.605**	0.711**	0.559**
PGA				
Baseline	0.746**	0.659**	0.649**	0.552**
After 6 mo	0.808**	0.804*	0.640**	0.676**
Pain Score				
Baseline	0.731**	0.644**	0.631**	0.539**
After 6 mo	0.811**	0.806**	0.644**	0.679**
PhGA				
Baseline	0.882**	0.867**	0.906**	0.849**
After 6 mo	0.810**	0.811**	0.881**	0.781**
ESR				
Baseline	0.591**	0.578**	0.635**	0.664**
After 6 mo	0.555**	0.577**	0.509**	0.508**
CRP				
Baseline	0.476**	0.607**	0.576*	0.691**
After 6 mo	0.590**	0.678**	0.631*	0.673**

TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, PhGA: physician global assessment, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. * $p < 0.05$; ** $p < 0.001$.

Dr. Leeb states that it is completely inappropriate to replace the PGA with the PhGA giving it *a priori* the same weighting within the formula. In the original DAS equation, the PGA is only minimally represented (being diminished by the constant 0.014), thus accounting for only 1-2% of the total score. We preferred to give the PhGA the same weight, especially as both are measured the same way.

Furthermore, our results revealed that (as shown in Table 3 in the study) PhGA correlated significantly with all disease activity measures, including PGA and pain score, both before and after treatment. Baseline PGA was not correlated with any of the 4 DAS effect sizes. PhGA showed the same finding except for the DAS3, with which it was positively correlated. Physician assessment was significantly correlated with the 4 DAS effect sizes within 6 months of initiation of therapy, with a higher "r" value than PGA, which showed a significant correlation with DAS1, 2, and 4, but with lower "r" values.

Regarding Dr. Leeb's comment about the use of EULAR response criteria for DAS variations being without validation, we believe there must be some misunderstanding. As the title of Table 2 (shown in the study) indicates, we assessed the average scores of DAS 2, 3, and 4 in relation to the cut off point of improvement in DAS1 (the original DAS). We also stated very clearly in the text that identification of cut off points of improvement for the new suggested DAS was beyond the scope of our study.

Finally, we do not agree that our work represents a step away from individualized patient oriented treatment. There are several causes for patient's pain that may vary from psychological to mechanical. The main target of treatment using both the expensive biologic therapy and/or DMARD is to induce disease remission. Optimization of therapeutic policy would only be achieved by proper assessment of disease activity. On the other hand, patient's satisfaction should be considered globally after assessment of all factors. In order to achieve such a difficult equation, we developed a multi-dimensional questionnaire that includes assessment for psychological, functional, joint, and systemic variables in addition to disease activity variables. We believe this is the best way to enhance treatment success.

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Tumor Necrosis Factor-α as a Potential Target in the Treatment of Systemic Lupus Erythematosus: A Role for the HMG-CoA Reductase Inhibitor Simvastatin

To the Editor:

In their excellent editorial, Shovman, *et al* have reviewed possible autoimmune mechanisms involved in the beginning and progression of atherosclerosis among patients with systemic lupus erythematosus (SLE)[1]. The phenomenon of premature atherosclerosis is a well known clinical entity from the mid-1970s, when Urowitz, *et al* described the so-called bimodal pattern of mortality and attributed the second peak of mortality to the premature atherosclerosis and its fatal cardiovascular complications[2]. Premature atherosclerosis in connective tissue disorders in general and in systemic lupus in particular was not explained well before Ross, who pointed out that the atherosclerotic process is inflammatory in its nature[3].

We reviewed the role of interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein-1 and pinpointed some promising therapeutic targets including tumor necrosis factor-α (TNF-α) blockade. The role of TNF-α in SLE is controversial. Some studies show a positive correlation between disease activity and TNF-α[4] and others do not[5]. Although TNF-α belongs to the group of TH1-dependent cytokines, and is recognized as a key cytokine in rheumatoid arthritis, several articles suggest that the level of TNF-α may reflect the level of inflammation in patients with SLE, and that these patients are characterized by a higher level of this cytokine compared to a healthy population[6]. On the other hand atherosclerosis itself is characterized by a high level of TNF-α and C-reactive protein that is produced in the liver in the response to cytokine stimulation. Therefore the idea of TNF-α blockade as the possible therapeutic target in lupus is very promising. In the same issue of *The Journal*, Yokota and colleagues[7] showed that simvastatin, a HMG-CoA reductase inhibitor, inhibits synthesis of IL-6 and IL-8 after TNF-α stimulation. To support results presented by the authors of both articles we present results of our preliminary study, where we focused on TNF-α as the potential therapeutic target in patients with SLE. Eight women aged 26–57 years (42 ± 10.3) fulfilling the American College of Rheumatology lupus criteria were enrolled. A group of 8 healthy women age matched to the patients served as controls. Lipid profile parameters including total, high density lipoprotein-cholesterol (HDL), and low density lipoprotein-cholesterol (LDL), triglyceride, and TNF-α concentration were measured. In the patients we also measured disease activity with the SLE Disease Activity Index (SLEDAI) scale. Additionally in the patients and controls the intima-media complex (IMC) measurements of both carotid arteries were done to detect the patients with subclinical atherosclerosis and exclude them. Then the patients were treated with simvastatin (20 mg/day) for 4 weeks. Before the study, patients with SLE showed very high levels of TNF-α compared to the controls. As expected, we showed lipid profile abnormalities with triglyceride, total and LDL cholesterol levels being higher and HDL cholesterol lower compared to the controls.

Twenty-eight days of treatment with simvastatin reduced LDL and total cholesterol and increased HDL cholesterol, but more importantly also prominently decreased TNF-α level in the sera of patients with lupus as compared to the period before study. We also observed decreased lupus activity in the SLEDAI scale. All results are summarized in Table 1.

The patients in our study were characterized by very high TNF-α levels that support the role of this cytokine in SLE and may indicate the blockade of TNF-α as a possible therapeutic target in the disease. The role of statins in lupus was suggested for the first time by Abud-Mendoza, *et al*, who showed beneficial effect of the drug in patients with drug-resistant lupus[8]. Due to their pleiotropic properties, statins interfere with inflammatory processes. These pleiotropic effects are realized via inhibition of geranylation of small G proteins, resulting in the restoration of the endothelium function and immunosuppressive and immunomodulatory activities[9].

Treatment with statins in lupus may be a unique opportunity to correct many risk factors with a single drug: to correct the lipid profile abnormalities often seen among patients with SLE, and at the same time to decrease inflammation as in atherosclerosis not evoked by autoimmune disorders. Statins seem to be good candidates for lupus-modifying drugs. They have been shown to limit progression of lupus nephropathy[8] and decrease the TNF-α concentration and disease activity in our pilot study. The more we know about the immune mechanism involved in progression of lupus and lupus-dependent atherosclerosis, the more therapeutic options we could apply. But before we decide to use cytokine-targeting therapy for lupus patients we should verify the usefulness of old drugs that are being successfully used in the treatment of atherosclerosis.

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Table 1. Characteristics of patients with SLE and healthy subjects.

Characteristics	Controls	Patients	
		Before Treatment	After Treatment
Total cholesterol, mg/dl	187 ± 38.4	221.75 ± 27.6	196.5 ± 21.9*
HDL cholesterol, mg/dl	55.9 ± 12.1	42 ± 12.2**	48.5 ± 14.9
LDL cholesterol, mg/dl	86.4 ± 11.7	137 ± 11.5**	103.8 ± 38.9*
Triglyceride, mg/dl	101 ± 34	193 ± 110	170.62 ± 103.4
TNF-α, pg/ml	7.4 ± 9.1	26.8 ± 29.3**	9.9 ± 7.06*
SLEDAI		14.6 ± 4.03	11.3 ± 3.85
IMC, mm	0.68 ± 0.06	0.64 ± 0.08	
Disease duration, mo (range)		22.8 (9–47)	

All values except disease duration are given as SEM ± SD. * Statistically significant compared to period before treatment ($p < 0.05$). ** Statistically significant compared to healthy counterparts ($p < 0.05$). SLEDAI: SLE Disease Activity Index.

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Dr. Shoenfeld replies:

To the Editor:

We appreciate the comments, results, and suggestions of Dr. Kotyla, *et al.* Indeed, despite the facts alluding to the important role of TNF-α in SLE by and large, and in the associated atherosclerosis[1], it seems that anti-TNF-α may still harbor some risks in some SLE patients and may result in induction of exacerbation. Therefore it seems very reasonable to use statins in SLE, because of their great diversity of immunomodulatory functions[2-12]. However, statins also may trigger or aggravate autoimmune diseases and several cases of statin-induced lupus have been reported[13,14]. Noel explained this phenomenon by the proapoptotic effect of the second generation of statins, whereas the release of nuclear antigens into circulation may foster the production of pathogenic antibodies[15]. Further knowledge regarding the use of statins routinely in SLE is needed.

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The Value of Temporal Artery Biopsy Specimen Length in the Diagnosis of Giant Cell Arteritis

To the Editor:

The article by Taylor-Gjevre and colleagues[1] on temporal artery biopsy (TAB) in patients with giant cell arteritis is of great interest because the presence of a reliable negative pathology report favors the diagnosis against giant cell arteritis (GCA) and may prevent unnecessary treatment with corticosteroids. In addition, TAB has a crucial role especially in situations in which clinical presentation is less characteristic. Skip lesions as short as 330 µm in length have been reported in GCA[2]. Therefore, many different strategies have been suggested to increase the sensitivity of TAB. Pless, *et al*[3] reported that bilateral TAB is 5% more likely than unilateral biopsy to detect the characteristic histopathologic findings in patients with GCA. However, in another study Danesh-Meyer, *et al*[4] reported that second TAB has a low yield of information in patients with suspected GCA if the specimens are adequate. Therefore, many suggestions for optimal length of TAB have been made from 2 to 7 cm[2,5-7].

According to the result obtained in this study the biopsies ≥ 10 mm length were more likely to be positive than those < 10 mm. This difference was statistically significant ($p = 0.037$) and subsequently achieving a minimum threshold of 10 mm biopsy length after formalin fixation was suggested to increase the diagnostic yield of TAB. It was very promising, as achieving a long biopsy segment is not always feasible. Sudlow[8] reported a median biopsy length of 10 mm in 200 TAB and the median length of TAB specimen in Chakrabarty and Franks'[9] study of 172 patients was 10 mm, which means that many of these biopsies can be relied on confidently in decision making. Therefore, we conducted a study on TAB specimen length of 117 patients between 1995 and 2004 at Southend Hospital NHS Trust to assess the value of biopsy length on diagnosis of GCA (Table 1).

From our data there is no statistically significant difference in positive result between biopsies ≥ 10 mm and those < 10 mm ($p = 0.94$). Raising or lowering the minimum threshold length did not approach a statistically significant difference in the rate of positive result. Positive and negative results were observed in specimens of different length (Figure 1).

Although there is a significant difference between harvested artery segments between different centers, our results did not support the threshold of 10 mm. A multicenter analysis with larger sample size is needed to elucidate the value of biopsy length in the diagnosis of GCA.

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Table 1. Demographic characteristics of patients with temporal artery biopsy.

Demographic Variable	Total Population	With Positive Biopsy	With Negative Biopsy
Number (%)	117	30 (26)	87 (74)
Sex (%)			
Male	37 (31.6)	9 (30)	28 (32.2)
Female	80 (68.4)	21 (70)	59 (67.8)
Age, mean ± SD yrs	73.66 ± 9.36	76.40 ± 7.26	72.72 ± 9.80
Mean length of TAB ± SD, mm (range)	11.95 ± 7.91 (2–60)	10.7 ± 5.61 (3–30)	12.37 ± 8.52 (2–60)
Mean length of TAB < 10 mm (%)	50 (43)	13	37
Mean length of TAB ≥ 10 mm (%)	67 (57)	17	50

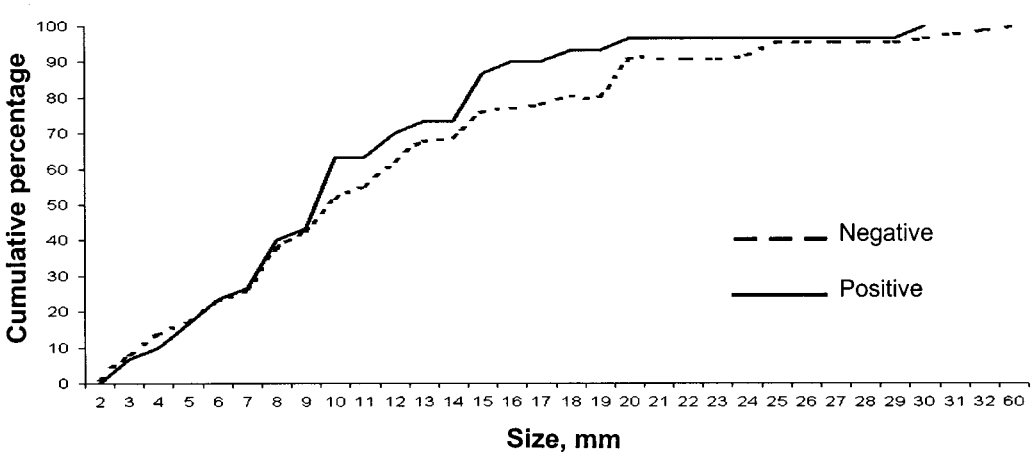

Figure 1. Temporal artery biopsy sizes for negative and positive specimens.

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Dr. Taylor-Gjevre replies

To the Editor:

We read Dr. Arashvand's correspondence with interest. Optimizing the diagnostic benefit that can be derived from a temporal artery biopsy (TAB) is highly desirable. The potentially discontinuous character of the histopathological changes, the skip lesions, has led to recommendations for optimal length of artery biopsy that has varied from 2 to 7 cm[1-3]. Frequently smaller artery biopsies are obtained despite these recommendations. The question whether these smaller specimens are of lower diagnostic yield is of clinical relevance. In our study, biopsy specimens that had been found to be positive for GCA after blinded pathology review tended to be longer than those found to be negative. However, we found a "threshold" length of 1.0 cm was associated with increased diagnostic yield in our sample[4]. Based on our data we recommend a post-formalin fixation length of 1 cm. In practical terms we feel this length is generally obtainable. Dr. Arashvand's review of their patient population found no diagnostic advantage for longer biopsies. With skip lesions reported historically in 28% of specimens[1], it is reasonable to consider a lower limit of biopsy length below which TAB sensitivity would drop. In our patient sample this was at 1 cm. This threshold may vary between centers and population samples. We agree a larger sample size would be beneficial in reviewing this question. Standardization of biopsy harvesting and processing techniques as well as pathologic interpretation would be important in such a study.

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Can Pain Be Quantified Numerically?

To the Editor:

Ritter, *et al*[1] proposed measuring pain with a visual numeric scale (VNS),

instead of with the more traditional visual analog scale (VAS). This is a good idea for the many reasons articulated, and so I agree that this represents a huge step in the right direction. One concern does remain, however. The authors speak of computing both change scores and means, something possible only with numerical data. But the inherent limitation on the precision with which pain can be measured, and the fact the data are neither measured nor counted, renders the data fundamentally non-numeric, despite the intention to treat the data as numeric.

This distinction between numeric and non-numeric is not mere semantics. Indeed, analyses based on assigning numerical scores to fundamentally non-numeric categories rely on specious precision and pseudo-information; such analyses have been shown to have poor properties when the data are either outcome measures[2] or predictors[3].

This statement does not in any way suggest that the VNS should not be used. Rather, a conservative analysis should be applied in which the numerical scores serve as labels only. The ordering among the categories would be considered by the analysis, but the relative spacings among the categories would not. No means or differences would be computed. Such conservative analyses have been shown to compare quite favorably to their overly optimistic counterparts[2,3].

For example, if post-randomization pain as measured by the VNS is the primary endpoint of a randomized clinical trial, and pain is collected also at baseline, then one would tabulate the data by treatment group as a 2-way 11 × 11 contingency table, with the 11 columns denoting the baseline score (0–10) and 11 rows denoting the subsequent score (also 0–10). The analysis would be based on the relative frequency of each of the 121 (11 × 11) possible shifts across treatment groups, and also consideration of which shifts are most indicative of patient improvement. See elsewhere for further details[3]. This conservative analysis strategy may appear to defeat the purpose of the VNS, but in fact it does not. The many benefits of the VNS relative to the VAS, as articulated by the authors[1], remain intact whether the data are treated as interval or ordinal. Moreover, there is a slippery slope from treating data as interval to treating data as normally distributed when they clearly cannot be. When non-normal data are treated as normal there is the distinct possibility of inflation of the false-positive (type I error) rate[4].

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Dr. Ritter replies

To the Editor:

Dr. Berger raises an important point regarding the VNS and ordered scales in general. In our experience, however, with enough cases and a well distributed range of responses, nonparametric and parametric tests will give essentially equivalent results[1]. This will not always be the case, and researchers should use care. For example, in small clinical trials or where the data are highly skewed, nonparametric methods such as suggested by Dr. Berger would be necessary. We thank him for raising this caution.

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Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome: Followup for Neoplasia

To the Editor:

We read with interest the recent article by Dr. Russell[1] reporting a slightly higher than expected rate of neoplasia in patients diagnosed with remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) syndrome, with a fairly long interval between onset of RS_3PE and diagnosis of cancer. Four cases of malignancies (non-Hodgkin's lymphoma, acute lymphocytic leukemia, male breast cancer, and squamous cell lung cancer) were observed in followup of 10 patients available from an original group of 25, diagnosed with RS_3PE before 1995[1].

We performed a similar study on a cohort of 20 patients diagnosed with RS_3PE before 1995. The criteria for diagnosis included abrupt onset of symmetrical painful swelling of both hands and/or feet associated with pitting edema, seronegativity for rheumatoid factor, absence of radiological abnormalities, prompt response to corticosteroid therapy, and resolution within 6–12 months with no sequelae. Followup data were available for 16 patients, whose mean age at onset of RS_3PE was 66 years (range 51–73). Two patients were reported by family to have died, one for myocardial infarction, the other for hemorrhagic stroke; and 2 remaining patients could not be reached. Of the 16 available patients, 3 had a cancer diagnosis following the recognition of RS_3PE: a woman was diagnosed with colon adenocarcinoma 8 months later, a man developed thyroid cancer 15 months afterward, and another man had prostatic adenocarcinoma 2 years later.

Compared with Russell's observations, we found a lower frequency rate of neoplasia and a shorter interval between the RS_3PE onset and cancer diagnosis. Moreover, the incidence of neoplasia among our patients with RS_3PE was similar to the rate reported from the Italian Association of Cancer Registries in a sex and age-matched population for the same period under study and the same geographic area[2].

RS_3PE is quite an intriguing syndrome whose paraneoplastic significance has been suggested in several reports[3-5].

We agree with Russell that studies on larger cohorts are needed to provide definite conclusions, and that patients with RS_3PE must be carefully monitored for neoplasia. However, in our longterm followup study on RS_3PE, we did not find a higher than expected rate of cancer.

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symmetrical synovitis with pitting edema (RS3PE): a form of paraneoplastic polyarthritis? J Rheumatol 1999;26:115-20.

Dr. Russell replies

To the Editor:

In response to the letter from Drs. Fietta and Manganelli describing their experience with longterm followup of patients with RS_3PE syndrome, I would agree larger cohort studies with longitudinal followup are indicated to resolve the issue of a relationship between RS_3PE and neoplasia. The small difference in intervals and incidence of cancer between our 2 followup studies underscores the lack of sufficient power statistically to draw conclusions about a cause and effect relationship. Notwithstanding such studies, it seems reasonable for physicians to have heightened awareness of a possible association with neoplasia when a patient presents with RS_3PE. These patients are often elderly and it would seem prudent to proceed with routine age and sex-appropriate cancer screening. However, the present lack of conclusive data does not justify more invasive testing without suggestive signs or symptoms that would warrant such. Ultimately, clarification of any relationship between RS_3PE and cancer awaits better understanding of the molecular pathophysiology of both, given the difficulty in doing large cohort studies of this rare syndrome.

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Inclusion of Patients in Randomized Controlled Trials

To the Editor:

Race and socioeconomic status (SES) are important characteristics of study populations in randomized controlled trials (RCT). Lee, *et al*[1] found no essential differences in factors influencing decisions to participate in rheumatoid arthritis (RA) RCT between Caucasians and the often under represented group of Hispanic patients, the former with a higher level of education and income. In the same issue, Dr. Hyrich and members of a consensus group investigating differences in patients recruited for RCT compared to routine practice[2] believe that patients recruited for trials are more likely to have higher SES; in turn this may be associated with better study results compared to clinical practice.

Both reports refer to observations from RCT in restricted geographical locations and emphasize the need to internationalize RCT thus increasing the diversity of study demographics. This would allow applicability of trial results to growing segments of affected populations. In Latin America, for example, RA RCT would include a vast majority of Hispanics with low or very low income and poor access to medical care and costly medications.

Factors such as race, education, and SES may influence disease outcome in patients with RA[3]. Evidence that these factors may influence results of RA RCT is lacking.

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Book Reviews

Osteoarthritis Handbook

Nigel Arden, Cyrus Cooper, editors. London: Taylor & Francis Group, 2006, 210 pages, $44.99 US.

New information regarding "the most common joint pathology worldwide" has been forthcoming continuously. This monograph is an attempt to harness that new information and put it into the foundation that already exists regarding osteoarthritis knowledge and research. In the main it succeeds in achieving this goal. This is a well written, evidence-based text by knowledgeable experts in their respective areas. In addition, it is richly referenced in all its chapters.

Highly recommended are the chapters regarding diagnosis (including imaging methods) and pharmacologic treatments. This latter chapter in particular is essential reading for the clinician who treats large numbers of patients with osteoarthritis. Treatments discussed range from acetaminophen to NSAID to topical and intraarticular therapies, glucosamine, and chondroitin. The presentation, in the format of background, safety profile, evidence, and summary, provides a balanced and effective overview of our understanding of the most common modalities in the management of osteoarthritis. Alternative and complementary approaches have been included in the chapter on nonpharmacological management; however, a more thorough discussion would have been timely and welcome, given the increasing interest in the (mis)information that is so prevalent in this regard. A succinct chapter on surgical treatment is well done and brings the reader up to date with new advances.

The book will serve the musculoskeletal consultant well, and the chapter on therapeutics should be required reading for any healthcare professional who is confronted by almost daily input from the media and patient confusion. The evidence-based approach will serve the clinician well, and as such, this monograph is a welcome addition to texts dealing with osteoarthritis.

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Canadian Residents' Rheumatology Handbook

Lori Albert, MD, editor. Victoria: Trafford Publishing, 2005, 223 pages, price $21.50 (US).

This handbook was put together by a postgraduate education committee of the Canadian Rheumatology Association and supported with an unrestricted educational grant from Pfizer Canada. The handbook is part of the course materials for a rheumatology curriculum for core medicine residents in Canada. It is a practical guide, rather than an exhaustive review of topics, for use in clinical settings. Each chapter ends with a few references for residents who want to pursue a subject in more detail.

This handbook aims to make medical residents confident and competent in identifying and managing common rheumatologic problems. Because of the shortage and maldistribution of rheumatologists in Canada, it is important for internists to be able to initiate the process of diagnosis and management before a rheumatologist can see the patient. The main

sections of the book are: Approach to Common Rheumatic Presentations (e.g., monoarthritis); Selection and Interpretation of Laboratory Tests and Imaging; Therapeutics; Selected Rheumatologic Emergencies; Physical Examination (screening and detailed joint examinations); and Joint Aspiration and Injection Techniques.

The chapters are structured uniformly, each beginning with "Key Concepts." Much of the book is in point form with prominent subtitles so that it is easy to find information. However, there are some omissions, e.g., in one table: pulmonary fibrosis under dermatomyositis and interstitial nephritis under Sjögren's syndrome. The use of generic and brand names for drugs is inconsistent. There are some undefined acronyms, such as "ARB." The clarity of the hand radiographs on pages 132-5 is not optimal.

I would certainly recommend the book to residents in internal medicine (and not just to Canadian ones), but also to first year rheumatology fellows, general internists, and family practitioners.

Howard Stein, MD, FRCPC, Rheumatologist, Honorary Professor, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.

Corrections

Mahr A, Artigues N, Coste J, Aouba A, Pagnoux C, Guillevin L, for the French Vasculitis Study Group. Seasonal variations in onset of Wegener's granulomatosis: Increased in summer? J Rheumatol 2006;33:1615–22. The correct Figure 2 is shown below. We regret the error.

Suissa S, Giroux M, Gervais M, et al. Assessing a whiplash management model: A population-based non-randomized intervention study. J Rheumatol 2006;33:581-7. The correct name of the sixth author is Joseph Austin Christopher Delaney. We regret the error.

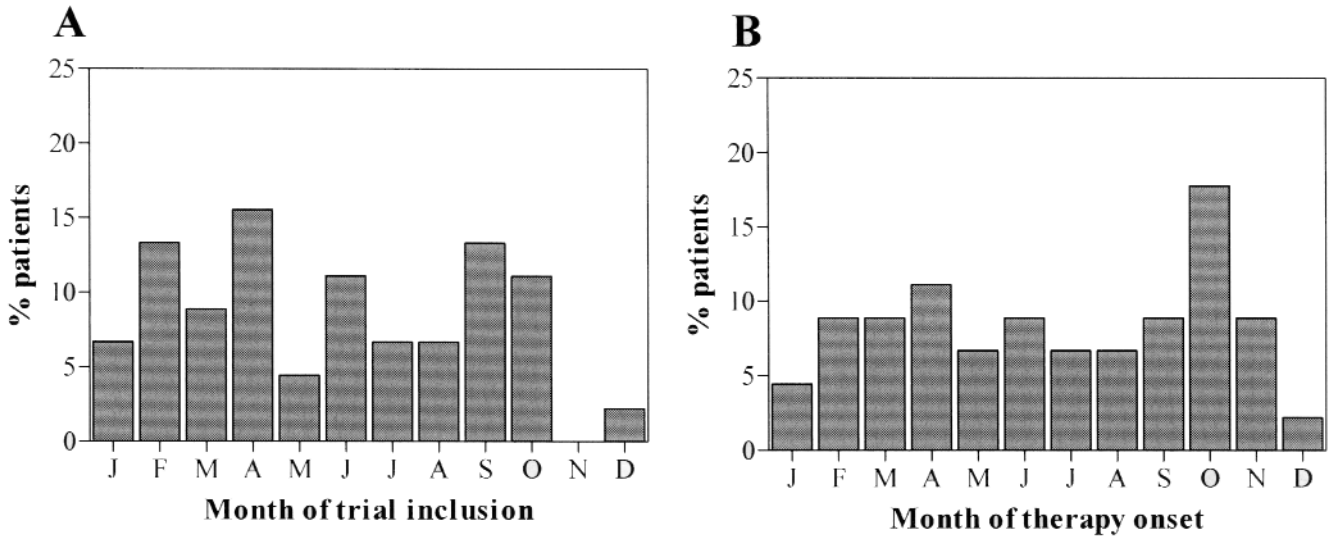

Figure 2. Distributions of trial inclusion (A) and therapy onset (B) by month for the 45 "informative" patients. A: chi-square 13.40, df 11, p = 0.28. B: chi-square 8.60, df 11, p = 0.69.