Lupus (2014) 23, 3–9

http://lup.sagepub.com

SPECIAL ARTICLE

The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics Classification criteria for systemic lupus erythematosus in two multiethnic cohorts: a commentary

GJ Pons-Estel[1,2], D Wojdyla[3], G McGwin Jr[2], LS Magder[4], MA Petri[5], BA Pons-Estel[6], on behalf of the Grupo Latino Americano De Estudio del Lupus (GLADEL) and GS Alarcón[2] on behalf of the LUMINA cohort

[1]Department of Autoimmune Diseases, Institut Clínic de Medicina i Dermatologia, Hospital Clínic, Spain; [2]Departments of Medicine, (Division of Clinical Immunology and Rheumatology) and Epidemiology, Schools of Medicine and Public Health, The University of Alabama at Birmingham, USA; [3]Escuela de Estadística, Universidad Nacional de Rosario, Argentina; [4]University of Maryland Dental School, USA; [5]Johns Hopkins University School of Medicine, USA; and [6]Hospital Provincial de Rosario, Argentina

The authors offer some comments on the advantages and possible drawbacks of using the SLICC criteria in longitudinal observational studies and clinical trials after applying and comparing them to the ACR criteria in two multinational, multiethnic lupus cohorts. *Lupus* (2014) **23,** 3–9.

Key words: Systemic lupus erythematosus; classification criteria; multiethnic cohorts; SLICC; ACR

Systemic lupus erythematosus (SLE) is probably the most important paradigm of systemic autoimmune disease and it is characterized by a wide spectrum of clinical manifestations and the presence of multiple autoantibodies. The disease has, in general, a variable course with periods of remission and flares eventually leading to different degrees of organ system damage and to a diminished survival.[1] Although significant advances in understanding its etiopathogenesis have been made over the last several years, the identification of patients with lupus depends on the clinicians' acumen and/or established criteria. Criteria are particularly important for longitudinal observational studies and clinical trials so that patients' recruitment can be accomplished in a systematic manner and patients compared across studies. With the advent and promise of new pharmaceuticals, this is particularly important. Efforts to establish criteria for the classification of SLE were first published by the American College of Rheumatology (ACR, then the American Rheumatism Association) in 1971,[2] revised in 1982[3] and updated, yet never validated, in 1997.[4]

Despite their worldwide use, many concerns have been voiced by clinicians and investigators in relation to these criteria: the lack of inclusion of many cutaneous and neurological manifestations, the omission of low complement levels and the impossibility of classifying as SLE patients with a biopsy-confirmed nephritis compatible with SLE (in the presence of lupus autoantibodies) but who did not have other criteria. The Systemic Lupus International Collaborating Clinics (SLICC) group decided to address these concerns and conducted a two-part study based on the evaluation of nearly 1400 patient scenarios or vignettes; this eight-year work of deriving and validating a new set of classification criteria for SLE culminated with their publication in 2012.[5] These criteria were noted to be more sensitive but less specific than the ACR criteria; they also resulted in fewer misclassifications of patients. The SLICC criteria have been received favorably by the lupus community,[6] including their endorsement by the European Medicines Agency.[7]

Correspondence to: Graciela S Alarcón, Department of Medicine, Division of Clinical Immunology and Rheumatology, School of Medicine, The University of Alabama at Birmingham, 520 20 St. S. Room 832, Birmingham, AL 35294, USA.

Email: galarcon@uab.edu

Received 28 September 2013; accepted 21 October 2013

10.1177/0961203313512883

At present, however, there are some important questions that need to be addressed: How do the SLICC criteria fare in other lupus registries and cohorts? Do they offer any advantage? Do they have any disadvantage? Should they be used in conjunction with the ACR criteria or instead of the ACR criteria? We have attempted to address some of these questions based on their application and comparison of their performance with the ACR criteria in patients from the LUpus in MInorities: NAture versus Nurture (LUMINA) and *Grupo Latino Americano De Estudio del Lupus* or Latin American Group for the Study of Lupus (GLADEL) cohorts. We will very briefly present these data and offer some comments.

Applying the criteria

Both the LUMINA and GLADEL cohorts have been amply described in the literature.[8–11] Suffice it to say that the LUMINA patients were recruited based on the updated 1997 ACR classification criteria whereas those of GLADEL were recruited based on the physicians' diagnosis; most patients fulfilled the ACR criteria although that was not a requisite. Of note, also, some clinical and immunological manifestations had not been collected in one or both of these cohorts and thus could not be included in these analyses (some acute and chronic forms of cutaneous lupus, non-scarring alopecia, toxic epidermal necrolysis, mononeuritis multiplex and complement values).

Two sets of comparisons were made. First, we compared the ACR criteria and the SLICC criteria in both cohorts. Second, we compared the physicians' clinical diagnosis and the SLICC criteria in the GLADEL cohort. In all cases, the goal was to determine which set of criteria would allow for an earlier patient classification particularly for those patients with lupus nephritis (LN). The statistical analyses were performed using SAS software version 9.1.3 for the LUMINA cohort (SAS Institute, Cary, NC, USA) and using SPSS software version 20.0 for the GLADEL cohort (SPSS, Chicago, IL, USA). Categorical variables were compared using Chi-square or modified Fisher exact tests, as appropriate.[12] Continuous variables were examined with analysis of variance (ANOVA). A p value < 0.05 was set as the level of statistical significance.

There were 640 patients in the LUMINA cohort at the time these analyses were performed; 18 patients (2.8%) did not meet the SLICC criteria despite a mean of 1.2 years from the time the ACR criteria were met and the time patients entered the cohort. Of the remaining 622 patients, 319 (51.3%) were classified at the same time using either criteria set, 78 earlier (12.5%, mean 0.7 years) and 225 (36.2%) later (mean 4.4 years) with the SLICC than with the ACR criteria. Five of the 78 earlier patients (6.4%) met the SLICC rule of LN plus one immunologic criterion. Of the patients classified later, the majority did so because of the combination of malar rash and photosensitivity into the single acute cutaneous lupus criterion. There were no differences in terms of age, gender and disease activity between these classification categories, but African Americans and Texan-Hispanics were more likely to be in the no difference category and Caucasians and Puerto Rican-Hispanics in the later or in the no diagnosis categories (data not shown). Table 1 shows the distribution of the SLICC criteria

Table 1 SLICC criteria in LUMINA cohort patients classified at the same time, earlier or later[a]

SLICC criteria	*SLICC criteria met at the same time, %* n = *319*	*SLICC criteria met earlier, %* n = *78*	*SLICC criteria met later, %* n = *225*	p *value*
Clinical				
Acute cutaneous lupus or SCLE	60.5	57.7	72.4	<0.001
Neurologic	16.9	11.5	4.9	<0.001
Leukopenia	79.0	85.9	62.2	<0.001
Thrombocytopenia	24.5	12.8	7.1	<0.001
Immunologic				
Anti-dsDNA	75.9	83.3	52.9	<0.001
Anti-Sm	56.1	73.1	24.0	<0.001
Anti-phospholipid	36.7	47.4	14.2	<0.001

SLICC: Systemic Lupus International Collaborating Clinics; LUMINA: LUpus in MInorities: NAture versus Nurture; SCLE: subacute cutaneous lupus erythematosus; Anti-dsDNA: anti-double-stranded DNA; Anti-SM: anti-Smith.
[a]Only the SLICC criteria that were significantly different in these three patient groups are shown.

among patients classified earlier, later and at the same time. Overall, there was an increased frequency of leukopenia and of anti-double-stranded DNA (anti-dsDNA), anti-Smith and antiphospholipid antibodies among those patients classified earlier, whereas there was an increased frequency of acute cutaneous lupus among those classified later; only those criteria that differ between the two sets are shown in Table 1. Table 2 depicts the ACR criteria among the same three patient categories. Malar rash and photosensitivity were more frequent among those classified later whereas no clear pattern emerged for those classified earlier. The presence of serositis, renal, neurologic, hematologic and neurologic criteria did not offer a distinctive advantage for the SLICC over the ACR criteria.[13]

Of the 1480 patients that constitute the GLADEL cohort, 81 (5.5%) patients were excluded from the analyses, 45 (3.0%) and 36 (2.4%) because they did not meet either the ACR or the SLICC criteria, respectively. The remaining 1399 patients were included in the comparison study; 850 (60.8%) were classified at the same time using either criteria set, 254 earlier with the SLICC criteria (18.2%) and 295 (21.1%) later. Fifty-four of the 254 earlier patients (21.3%) met the SLICC rule of LN plus one immunologic criterion. There were no differences in terms of gender, ethnicity and disease activity between these categories but patients in the ''later'' category were somewhat younger at diagnosis than patients in the ''earlier'' and ''same time'' categories (data not shown). Table 3 shows the distribution of the SLICC criteria among patients classified earlier, later and at the same time. Overall, there was an increased frequency of integument manifestations among patients classified later but a clear pattern among those classified earlier or at the same time did not emerge; only those criteria that differ between the two sets are shown in Table 3. Table 4 depicts the ACR criteria among the same three patient categories. Overall integument manifestations were more frequent among patients classified as later but no distinctive features were appreciated among those classified earlier or at the same time.[14]

Finally, since patients were recruited into the GLADEL cohort according to an experienced physician's diagnosis, we were interested in determining whether the SLICC criteria offered any advantage over the ACR criteria. In fact the proportion of patients classified earlier, later or at the same time was comparable using either set of criteria: 32.5% vs 30.4% for earlier, 19.1% vs 18.1% for later and 48.4% vs 51.5%. Table 5 shows the distribution of the SLICC criteria in patients classified earlier, later and at the same time than the physician's diagnosis. Acute cutaneous lupus, leukopenia, renal involvement and oral ulcers occurred with increased frequency among patients classified later but no distinctive features were evident among those classified earlier or at the same time.[15]

Comments

We found the SLICC criteria to apparently perform better in the GLADEL cohort than in the LUMINA cohort as there was a higher proportion

Table 2 ACR criteria in LUMINA cohort patients as per categories of the SLICC criteria at enrollment: Same, earlier and later

ACR criteria	*SLICC criteria met at the same time, %* n = *319*	*SLICC criteria met earlier, %* n = *78*	*SLICC criteria met later, %* n = *225*	p *value*
Malar rash	46.1	30.8	57.3	<0.001
Discoid rash	13.2	9.0	11.1	0.757
Photosensitivity	40.8	48.7	64.9	<0.001
Oral ulcers	42.6	38.5	39.6	0.785
Synovitis	76.5	74.4	76.0	0.506
Serositis	51.1	28.2	35.1	<0.001
Renal	38.6	29.5	24.4	<0.001
Neurologic	13.8	5.1	4.4	<0.001
Hematologic	75.9	70.5	60.0	<0.001
Immunologic	83.4	65.4	59.1	<0.001
ANA	97.2	100.0	99.1	0.510

ACR: American College of Rheumatology; LUMINA: LUpus in MInorities: NAture versus Nurture; SLICC: Systemic Lupus International Collaborating Clinics; ANA: antinuclear antibody.

Table 3 SLICC criteria in GLADEL cohort patients classified as SLE at the same time, earlier or later[a]

SLICC criteria	*SLICC met at the same time, %* n = *850*	*SLICC criteria met earlier, %* n = *254*	*SLICC criteria met later, %* n = *295*	p *value*
Clinical				
Acute cutaneous lupus or SCLE	77.4	67.3	90.2	<0.001
Chronic cutaneous lupus	11.3	7.9	22.4	<0.001
Oral ulcers	41.8	36.2	65.1	<0.001
Synovitis	83.8	81.5	90.2	0.009
Renal	53.1	48.4	58.6	0.054
Hemolytic anemia	14.1	8.3	11.9	0.044
Thrombocytopenia	22.1	24.4	30.5	0.015
Immunologic				
Direct Coombs test	56.9	35.1	54.9	0.054

SLICC: Systemic Lupus International Collaborating Clinics; GLADEL:Grupo Latino Americano De Estudio del Lupus; SLE: systemic lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus. [a]Only the SLICC criteria that were significantly different in these three patient groups are shown.

Table 4 ACR criteria in GLADEL cohort patients as per categories of the SLICC criteria at enrollment: Same, earlier and later

ACR criteria	*SLICC criteria met at the same time, %* n = *850*	*SLICC criteria met earlier, %* n = *254*	*SLICC criteria met later, %* n = *295*	p *value*
Malar rash	53.1	28.0	78.0	<0.001
Discoid lupus	8.1	5.1	19.0	<0.001
Photosensitivity	50.5	29.1	67.1	<0.001
Oral ulcers	29.3	17.3	57.3	<0.001
Synovitis	75.8	65.4	84.7	<0.001
Serositis	20.6	14.6	25.8	0.028
Renal	35.2	23.2	37.6	<0.001
Neurologic	7.1	6.3	8.1	0.698
Hematological	56.4	41.3	59.0	<0.001
Immunologic	59.2	53.5	41.7	<0.001
ANA	98.3	98.7	92.9	<0.001

ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics; GLADEL:Grupo Latino Americano De Estudio del Lupus; ANA: antinuclear antibodies.

of patients classified earlier in GLADEL than in LUMINA (18.2% vs 12.5%). Furthermore, the SLICC criteria performed better than the physicians' diagnosis since the proportion of patients classified earlier was even higher in this comparison (30.4%) as noted in Table 5. The apparent advantage of GLADEL over LUMINA can be explained by the fact that patients were recruited into the LUMINA cohort only if they already met four ACR criteria; consequently patients with LN and lupus autoantibodies and/or those with only three criteria could not have been part of this cohort. The SLICC criteria clearly offer some advantages over the ACR criteria. First, using the SLICC criteria we were able to classify as having lupus, patients with biopsy-proven nephritis (as defined by the International Society of Nephrology/Renal Pathology Society 2003 classification of LN[16]), in the presence of a positive autoimmunity (antinuclear antibodies (ANAs) and/or anti-dsDNA antibodies). This early diagnosis could lead to the implementation of a prompt and aggressive treatment aimed not only at preventing renal damage, one of the most important predictors of mortality in SLE patients,[17–19] but at the inclusion of such patients in randomized clinical trials that is not possible at the present time using the ACR criteria. This is a very practical and important consideration given the pace at which this field is now moving.

Table 5 SLICC Criteria in GLADEL cohort patients categorized as having SLE according to the physicians' diagnosis

SLICC criteria	*SLICC diagnosis met at the same time, %* N = *733*	*SLICC diagnosis met earlier, %* N = *432*	*SLICC diagnosis met later, %* N = *257*	p *value*
Clinical				
Acute cutaneous lupus	76.3	74.5	84.8	0.005
Chronic cutaneous lupus	13.6	12.7	16.7	0.324
Oral ulcers	43.2	43.3	52.9	0.019
Nonscarring alopecia	64.3	65.5	61.1	0.499
Synovitis	81.6	85.6	86.8	0.067
Serositis	31.7	29.9	35.0	0.371
Renal	52.8	48.1	59.9	0.011
Neurologic	20.2	25.2	23.3	0.123
Hemolytic anemia	14.9	10.9	9.7	0.040
Leukopenia	72.7	69.4	78.2	0.044
Thrombocytopenia	23.1	25.9	26.8	0.359
Immunologic				
ANA	99.7	99.3	97.9	0.015
Anti-dsDNA	75.0	71.4	75.9	0.379
Anti-Sm	51.6	52.1	45.4	0.447
Antiphospholipid antibody	55.3	57.9	59.4	0.605
Low complement	70.4	66.7	72.2	0.299
Direct Coombs test	55.3	48.8	57.4	0.545

SLICC: Systemic Lupus International Collaborating Clinics; GLADEL:Grupo Latino Americano De Estudio del Lupus; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies; Anti-dsDNA: anti-double-stranded DNA; Anti-SM: anti-Smith.

Second, a more balanced and clinical representation of each organ systems is achieved with the SLICC than with the ACR criteria, that is, they have better face validity. An important example is constituted by the mucocutaneous manifestations which are somewhat overlapping (photosensitivity and malar rash) in the ACR criteria. In contrast, in the SLICC criteria these and many other mucocutaneous manifestations have been grouped under acute cutaneous lupus, chronic cutaneous lupus and oral ulcers. This may prevent patients with purely cutaneous lupus to be classified as systemic lupus while allowing the inclusion of other patients under the category of systemic if, in addition to these cutaneous manifestations, they meet the total number of criteria required (still four, but importantly there has to be at least one clinical criterion and one immunological criterion present). Along these lines, the inclusion of neurological manifestations over and above psychosis and seizures (such as mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state), of hypocomplementemia within the immunological criterion and of each hematologic manifestation individually (hemolytic anemia, leukopenia/lymphopenia, and thrombocytopenia) enables us to classify as SLE patients who could not be classified as such using the ACR criteria allowing them to access specialized care earlier thus avoiding the negative consequences of late referrals and delays in the implementation of adequate treatments.[20]

Third, this set of criteria when compared to the judgment of expert physicians also allowed the earlier diagnosis of a sizable proportion of patients who, otherwise, could not be identified until later with the consequent beneficial implications already noted. It is of interest, however, that when a similar analysis was carried out with the ACR criteria similar proportions of patients classified earlier were observed.

Still this set of criteria is far from perfect; one of the most important disadvantages is the distinct possibility that some patients could not be identified until later using the SLICC criteria, and some, not at all; this tendency seems to relate to the fact that malar rash and photosensitivity fall within the acute cutaneous lupus category and thus count as only one criterion.

Our study has some important limitations that are worth pointing out. First and as already noted, all patients in the LUMINA cohort have satisfied the ACR criteria to enter the cohort; so patients with fewer than four criteria were not eligible for LUMINA and thus we do not know whether they could have been classified as lupus with the

SLICC criteria. Second, not all the clinical manifestations included in the SLICC criteria had been obtained/recorded in these two patient registries. Finally, the date at which each SLICC or ACR criteria manifestation had occurred was based on the existent data on each one of the cohorts; it is possible that these dates may not have the precision that could had been derived from obtaining these data with the specific purpose of assessing the ACR and the SLICC criteria.

So, how will we classify patients as meeting or not meeting criteria for SLE mindful of the implications such classification represents to patients and researchers alike? Should we use both sets of criteria concurrently/simultaneously in longitudinal observational studies and clinical trials? In our view, the jury is still out. What further actions should/could be taken to arrive at sound conclusions? Will similar studies need to be conducted in other cohorts/registries? The final answer can come only from conducting studies in which patients suspected of having lupus and related disorders are studied and followed over time according to a specified protocol; this will overcome the problems we encountered when applying them to the LUMINA and GLADEL cohorts. For such studies all laboratory tests should be conducted at central laboratories to allow for comparability; this requirement will make them exceedingly expensive and may not be considered a priority by funding agencies and thus they may never come to fruition. So what we have is not ideal but it is close to it. As pointed out in the original publication, the SLICC criteria retain the simplicity of the ACR criteria and also reflect the knowledge in understanding lupus gained in the almost three decades since they were published.[5]

Funding

This work was supported by grants from the Federico Wilhelm Agricola Foundation Research (BAPE), the STELLAR (Supporting Training Efforts in Lupus for Latin American Rheumatologists) Program funded by Rheuminations Inc and the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)-Beca de Formació i Contractació de Personal Investigador (GPE).

Conflict of interest statement

The authors have no conflicts of interest to declare.

Author contributions

All authors were involved in drafting or revising this article critically for important intellectual content, and all authors approved the final version to be published. Drs Graciela S. Alarcón and Gerald McGwin Jr (LUMINA), Daniel Wojdyla (GLADEL), Dr Guillermo J. Pons-Estel (LUMINA and GLADEL), and Dr Bernardo A. Pons-Estel (GLADEL) have full access to all of the data from the study and take responsibility for their integrity and the accuracy of the analyses performed.

Acknowledgments

We are grateful to Daniel Villalba and Leonardo Grasso for providing expert assistance with the ARTHROS (version 6.0) software.

References

1 Agmon-Levin N, Mosca M, Petri M, Shoenfeld Y. Systemic lupus erythematosus one disease or many? *Autoimmun Rev* 2012; 11: 593–595.
2 Cohen AS, Reynolds WE, Franklin EC, *et al*. Preliminary criteria for the classification of systemic lupus erythematosus. *Bull Rheum Dis* 1971; 21: 643–648.
3 Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271–1277.
4 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
5 Petri M, Orbai AM, Alarcón GS, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64: 2677–2686.
6 Cervera R, Espinosa G. Connective tissue diseases: Classification criteria for SLE: The latest—but not least—attempt. *Nat Rev Rheumatol* 2012; 8: 506–507.
7 European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus, cutaneous lupus and lupus nephritis, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139615.pdf (2013, accessed 17 August 2013).
8 Alarcón GS, Friedman AW, Straaton KV, *et al*. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. LUpus in MInority populations: NAture vs. Nurture. *Lupus* 1999; 8: 197–209.
9 Pons-Estel BA, Catoggio LJ, Cardiel MH, *et al*. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: Ethnic and disease heterogeneity among "Hispanics". *Medicine (Baltimore)* 2004; 83: 1–17.
10 Burgos PI, McGwin G Jr, Reveille JD, Vilà LM, Brown EE, Alarcón GS. Is familial lupus different from sporadic lupus? Data from LUMINA (LXXIII), a multiethnic US cohort. *Lupus* 2010; 19: 1331–1336.
11 Alarcón-Segovia D, Alarcón-Riquelme ME, Cardiel MH, *et al*. Familial aggregation of systemic lupus erythematosus,

rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis Rheum* 2005; 52: 1138–1147.
12 Fisher exact probability test: 2×3, http://www.vassarstats.net/fisher2x3.html (accessed 18 September 2013).
13 Alarcón GS, McGwin G Jr, Madger LR, Petri M. Comparing the ACR and the SLICC criteria for the classification of SLE patients using data from an existing multi-ethnic cohort. *Arthritis Rheum* 2012; 64: S262.
14 Pons-Estel GJ, Wojdyla D, Soriano ER, *et al*. Comparison of the ACR and the SLICC criteria for the classification of SLE patients using data from a multiethnic Latin American cohort. *Lupus* 2013; 22(Suppl 1): 63.
15 Pons-Estel GJ, Wojdyla D, Catoggio LJ, *et al*. Comparing the physicians diagnosis and the SLICC criteria for the classification of SLE patients using data from a multiethnic Latin American cohort. *Lupus* 2013; 22(Suppl 1): 56.
16 Weening JJ, D'Agati VD, Schwartz MM, *et al*. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241–250.
17 Danila MI, Pons-Estel GJ, Zhang J, Vilà, Reveille JD, Alarcón GS. Renal damage is the most important predictor of mortality within the damage index: Data from LUMINA LXIV, a multiethnic US cohort. *Rheumatology (Oxford)* 2009; 48: 542–545.
18 Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. *Arthritis Rheum* 2013; 65: 2154–2160.
19 Mak A, Cheung MW, Chiew HJ, Liu Y, Ho RC. Global trend of survival and damage of systemic lupus erythematosus: Meta-analysis and meta-regression of observational studies from the 1950s to 2000s. *Semin Arthritis Rheum* 2012; 41: 830–839.
20 Souza DC, Santo AH, Sato EI. Trends in systemic lupus erythematosus mortality rates in the state of Sao Paulo, Brazil from 1985 to 2004. *Clin Exp Rheumatol* 2010; 28: 519–524.