PostScript

MATTERS ARISING

If you have a burning desire to respond to a paper published in the *Annals of the Rheumatic Diseases*, why not make use of our "rapid response" option?

Log on to our website (www.annrheumdis.com), find the paper that interests you, and send your response via email by clicking on the "eletters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eletters" on our homepage.

The editors will decide as before whether also to publish it in a future paper issue.

Classification criteria for Sjögren's syndrome

I read with great interest the editorial by R Manthorpe published in the June issue of the *Annals of the Rheumatic Diseases*.¹ The author reviewed the different criteria that have been proposed for the classification of patients with Sjögren's syndrome (SS) and, in particular, commented on the US-European Consensus Group criteria,² which were reported for the first time in this same issue. As the first author of the paper, I would like to discuss certain points and criticisms which he raised about our criteria set. First of all I would like to discuss briefly the meaning of "classification criteria" and the methods by which the European^{3,4} and US-European criteria for SS² were derived.

Classification criteria are not meant to be used for diagnosis. Diagnosis is an often complex process by which a doctor arrives at the suspicion of a specific disease in a given patient, and then must collect enough clinical data to confirm that suspicion. Classification criteria, on the other hand, represent a tool for research and communication, providing uniform criteria for the scientific community to classify patients with the same disease, select patients for clinical-therapeutic trials, and make the data obtained by different researchers in different series of patients comparable. As any experienced rheumatologist knows, it is not uncommon to diagnose a specific rheumatic disease in a patient who does not meet the classification criteria proposed for that disease.

Given these considerations we can argue that:

- Classification criteria can be used for diagnostic purposes only when they have a sensitivity and specificity of 100%
- Because none of the classification criteria for systemic rheumatic diseases reach this level of sensitivity and specificity, it is evident that some patients with a given disease will fail to be classified as having it, and some normal controls may be erroneously classified as patients with that disorder

- Given the purpose of classification criteria, it is preferable to adopt criteria with a specificity approaching the optimum (100%), which would reduce to a minimum the possibility of including false positive controls, but without an excessive loss of sensitivity, which might result in the exclusion of large numbers of true patients.

The only objective method to derive classification criteria is to evaluate, in a series of patients with a given disease and in normal controls, the sensitivity/specificity ratio of different diagnostic tools for that disease, and then to select the combination of these which shows the highest accuracy in correctly classifying cases. Patients and controls should have been preliminarily diagnosed on the basis of a "gold standard". Because for the systemic rheumatic diseases a "gold standard" does not exist, the only standard, which can be adopted, is the clinical diagnosis made by an experienced specialist. This in fact was the procedure adopted by the American College of Rheumatology to define the classification criteria for rheumatoid arthritis⁵ and by the European Community Group to define³ and validate⁴ those for SS. This method is naturally far from perfect, because the pre-definition of the groups of true patients and true controls will invariably be influenced by the clinical data which are available at the moment of the preliminary evaluation and selection of cases. The fact that in our study the numbers of patients and controls were quite large and were collected from different centres in different countries nevertheless offers some assurance that any bias in the selection process would have been extremely diluted, and that the entire disease spectrum was covered. Despite these well known limitations, this method remains the only satisfactory one for defining and validating classification criteria.

The only alternative is to establish classification criteria based on the suggestions of a group of experts. However, these criteria would still have to be validated in clinically defined groups of patients and controls in order to determine their sensitivity and specificity.

In any case, once populations of "true patients" and "true controls" have been selected, the definition of a classification criteria set becomes a purely statistical operation—that is, one of choosing a set of diagnostic tests and finding the combination which shows the best sensitivity/specificity ratio.

If these points are kept in mind, most of the criticisms about the US-European classification criteria for SS fall to the ground. The definitions of item III (ocular involvement) and item V (salivary gland involvement) as the presence of one positive test, and that of item IV (histopathology) as the presence of a focus score = 1, are not merely definitions suggested by an expert committee. They were, on the contrary, arrived at after rigorous statistical analysis of a large series of patients and controls, and by testing the sensitivity/specificity ratio of all the possible items and combinations thereof. Moreover, the application of a purely statistical procedure guarantees that completely interdependent variables

were excluded by the procedure itself. There are many data indicating that autoantibody production and lymphocyte infiltration in the minor salivary glands are related,⁶ but statistically speaking the inclusion of both items in the classification criteria improved the performance of the whole set, with respect to their mutual exclusion.

The inclusion of symptoms (items I and II) allows the researcher to start with a simple questionnaire in selecting potential patients with SS, a point which is of great interest for epidemiological surveys. On the other hand, I would entirely agree that a limited number of patients with SS deny having any symptoms. To avoid the misclassification of these non-symptomatic patients, the US-European Consensus Group tested and added an additional criterion for primary SS—namely, three positive results out of the four objective items.

A rigorous statistical method was also followed to define the sequence of items in classification tree procedure. I agree that to perform the autoantibody determination (item VI) before lip biopsy (item IV) appears more logical from the clinical point of view and more acceptable for the patient. However, this was not suggested by the statistical results in order to obtain the best performance of the procedure as whole.

Keeping in mind the statistically derived European classification criteria and using the European database for new statistical analysis, the US-European Consensus Group decided to introduce some modifications in the criteria set. These modifications were particularly designed to (a) more precisely define the individual criteria items; (b) revise the list of exclusion criteria for primary SS; and (c) attempt to improve the specificity of the criteria.

Manthorpe's conclusion that the US-European classification criteria can only correctly classify a subgroup of patients with SS is not confirmed by the results of our statistical analysis. By testing previously proposed criteria for SS in our European populations of patients and controls,⁴ we showed that the accuracy of the European classification criteria was significantly higher than all of the others. The accuracy of the Copenhagen criteria,⁷ for example, was found to be 85.6% compared with 96.9% for the European set ($p < 0.005$), a difference that can be ascribed to the low sensitivity (71.4%) rather than the quite good specificity (93.5%) of the former. This means that more than a quarter of patients with clinically defined SS cannot be correctly classified using the Copenhagen criteria. It is worth noting that the modifications introduced in the proposed US-European version of the criteria do not absolutely reduce their accuracy with respect to that of the European criteria²; the analysis of the receiver operating characteristic curve showed a slight increase in specificity with a corresponding loss of sensitivity. This in fact represents an improvement when the purpose of classification criteria is considered.

C Vitali

Department of Internal Medicine and Section of Rheumatology, "Villamarina" Hospital, Piombino, Italy

Correspondence to: Dr C Vitali, Department of Internal Medicine and Section of Rheumatology, "Villamarina" Hospital, via Forlanini, 57025 Piombino, Italy; hyqprgbv@tin.it

References

- 1 **Manthorpe R.** Sjögren's syndrome criteria. American-European and Japanese groups' criteria compared and contrasted. *Ann Rheum Dis* 2002;61:482–4.
- 2 **Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al.** Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.
- 3 **Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al.** Preliminary classification criteria for Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;36:340–7.
- 4 **Vitali C, Bombardieri S, Moutsopoulos HM, Coll J, Gerli R, Hatron PY, et al.** Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases. Results of a prospective multicentre study. *Ann Rheum Dis* 1996;55:116–21.
- 5 **Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al.** The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
- 6 **Gerli R, Muscat C, Giansanti M, Danieli MG, Sciuto M, Gabrielli A, et al.** Quantitative assessment of salivary gland inflammatory infiltration in primary Sjögren's syndrome: its relationship to different demographic, clinical and serological features of the disorder. *Br J Rheumatol* 1997;36:969–75.
- 7 **Manthorpe R, Oxholm P, Prause JU, Schiödt M.** The Copenhagen criteria for Sjögren's syndrome. *Scand J Rheumatol Suppl* 1986;61:19–21.

Author's response

Claudio Vitali has provided a valuable historical background to his comments on the European Sjögren's syndrome (SS) criteria. To this part there is only a little to add. Although classification criteria are not meant to be used for diagnosis, discussions and talks with colleagues at various congresses world wide have shown that this is unfortunately not so in practice, neither in scientific trials nor in publications. Under ideal circumstances there should be only small differences—if any—between classification criteria and diagnostic criteria. It is not an easy task to tell a patient that she has SS when participating in this scientific project but otherwise she is not considered to have SS—or vice versa. It was with the same arguments that most Europeans discarded the terminology probable/definite SS. Progress within clinical science—including SS—is usually a continuous process but occasionally bigger strides are made. When leading SS scientists from America (US) and Europe (Eur) formed a consensus group to propose a new set of criteria for SS it was expected that they would include the latest news within the SS area—or that at least the news would be discussed and commented upon. The consensus group failed in this important aspect and this was the reason, therefore, why my leader had the subtitle: "American-European and Japanese Groups' criteria compared and contrasted", especially as the Japanese SS researchers came up with rather different results, which were based upon data from more patients/cases.¹ From a clinical point of view the Japanese III criteria are of great importance and seemingly more relevant.

One important factor of the Japanese III criteria is that they do not operate with or include subjective symptoms because their statistical calculations showed that it did not improve their results.¹ This is in contrast with the US-Eur consensus group which continues to include ocular (item I) and oral (item III) dry symptoms—unchanged from 1993. Research has shown that even though the cornea is the most densely innervated organ, there are no nerves which can register dryness. To include dry eyes in the criteria is therefore inappropriate. (Dry eyes is an iatrogenic expression which some patients are very quick to adopt.)

Another important contrast between the US-Eur consensus group and the Japanese expert group is that the latter requires at least two abnormal ocular tests for the function of the lacrimal gland to confirm the diagnosis keratoconjunctivitis sicca and two abnormal oral tests for the function of the salivary glands to confirm the diagnosis stomatitis sicca.¹ However, sialography can stand alone.¹ The US-Eur group requires only one test, which in practice is an abnormal Schirmer-I test (≤ 5 mm in 5 minutes performed without anaesthesia and with closed eyes) for the lacrimal gland and an abnormal unstimulated whole sialometry (≤ 1.5 ml in 15 minutes performed without tobacco, eating, and drinking during the preceding two hours) for the salivary gland. (It is usually customary to get a "confirmatory" test result when the findings are abnormal, as in HIV.) In the leader I expressed concern about the proposal that three positive results out of four objective items in an asymptomatic patient should automatically be called primary SS. If the abnormal items are IV, V, and VI, there is no proof that the lacrimal gland is also affected.

Probably the greatest "negative" scientific point of discussion was the lack of comments on the observation previously published in this journal that the number of cigarettes smoked per week may have a tremendous effect on the result of the focus score in lower lip biopsy (item IV) as well as on the level of anti-SSA/B autoantibodies (item VI).² In historical non-smokers the results in item IV and VI were statistically significant compared with those found in present and/or past smokers.² In the last group it did not matter if the date at which they stopped was recent or several years (decades) previously. The smoking effect was highly dose dependent, with the threshold around 21 cigarettes a week.² Consider the number of people with irritation of the eyes and dryness in the mouth who are/have been smokers and thus might not fulfil item IV or item VI of the US-Eur consensus group. If they nevertheless have at least two abnormal functional test results from both the lacrimal and the salivary glands, I find it today medically, ethically, and morally wrong not to accept that these patients have primary SS. Research in the autoimmunity/tobacco area seems only to be in its infancy.³

In conclusion, I cannot advise colleagues to start using the US-Eur consensus group criteria for SS uncritically. A big step towards obtaining longstanding international SS criteria was taken at the VIII International SS Symposium in Kanazawa, Japan 2002, when great acclamation was given to a proposal to form a big international SS consensus group. It is to be hoped, that this group of SS researchers from Japan, China, Europe, and America will some day, and the sooner the better, deliver their view(s)—unless we could have an earlier 100% diagnostic test in our

hands—valid for smokers, ex-smokers, and "never" smokers.

R Manthorpe

Sjögren's Syndrome Research Centre, Department of Rheumatology, Malmö University Hospital, SE-205 02 Malmö, Sweden

Correspondence to: Dr R Manthorpe; Manthorpe@inet.uni2.dk

References

- 1 **Fujibayashi T, Sugai S, Miyasaki N, Tojo T, Miyawaki S, Ichikawa Y, et al.** Criteria for the diagnosis of Sjögren's syndrome (Japanese criteria III). Supported by the Ministry of Health and Welfare of Japan. 1999 *Annual reports of the research group of autoimmune disease* 1999:35–8.
- 2 **Manthorpe R, Benoni C, Jacobsson L, Kirtava Z, Larsson Å, Liedholm R, et al.** Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjögren's syndrome? *Ann Rheum Dis* 2000;59:54–60.
- 3 **Sopori M.** Effects of cigarette smoke on the immune system. *Nat Rev Immunol* 2002;2:372–7.

Etanercept treatment of rheumatoid arthritis in the "real world"

A recent paper in the *Annals of the Rheumatic Diseases* attempted to examine the "real world" experience of etanercept treatment by examining the incidence of flares of rheumatoid arthritis (RA) disease activity in a cohort of patients with RA who had started treatment with etanercept before September 1999.¹ The number of flares and patients experiencing flares within the first year of etanercept treatment was compared with that seen in the same cohort of patients the year before they started etanercept. It is well documented that the withdrawal rate from disease modifying antirheumatic drug (DMARD) treatment in RA increases with the length of time the patient has been receiving the drug and that a number of these withdrawals relate to loss of efficacy.^{2–4} Therefore, it is reasonable to assume that the number of disease flares will increase the longer a patient with RA is receiving treatment, particularly if that treatment is failing to control the disease activity. The fact that treatment of this cohort of patients with RA was changed to etanercept suggests that their current DMARD treatment was failing to control their disease. Therefore it is likely that there would be an increased number of disease flares in this group before starting etanercept treatment. Although not stated in the paper, it is reasonable to assume that this cohort of patients with RA had been receiving their previous DMARD treatment for some time before changing to etanercept treatment. Therefore what the authors of this paper have compared is the number of RA disease flares in a cohort of patients with RA in their first year of etanercept treatment with the number of RA flares in their last year of (failing) DMARD treatment. The results are predictably in favour of the new treatment.

Would the authors have found the same results in favour of etanercept treatment if they had conducted a "fairer" comparison and compared the number of flares in this RA cohort during their first year of the previous DMARD treatment, especially if it was methotrexate, with the first year of etanercept treatment?

M D Smith

Rheumatology Research Unit, Repatriation General Hospital, Daws Road, Daw Park South Australia 5041

Correspondence to: Professor M D Smith; malcolm.smith@rgh.sa.gov.au

References

- 1 **Yazici Y**, Erkan D, Kulman I, Belostocki K, Harrison MJ. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". *Ann Rheum Dis* 2002;61:638–40.
- 2 **Wluka A**, Buchbinder R, Mylvaganam A, Hall S, Harkness A, Lewis D, *et al.* Long term methotrexate use in rheumatoid arthritis: 12 year followup of 460 patients treated in community practice. *J Rheumatol* 2000;27:1864–71.
- 3 **Maetzel A**, Wong A, Strand V, Tugwell P, Wells G, Bombardier C. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology (Oxford)* 2000;39:975–81.
- 4 **Wolfe F**, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990;17:994–1002.

Authors' reply

We thank Dr Smith for his interest in our recent publication. In his comments he states that it is well documented that the withdrawal rate from disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) treatment is increased with increasing duration of use. He therefore suggests that our study design biases our results because by using patients who have changed their DMARD, we have selected those for whom the usefulness of that particular drug has been outlived. However, we contend that although the withdrawal rate from DMARDs increases with time, this may be a consequence of increasing disease severity and RA refractoriness, and not simply lost effectiveness of the drug.

The natural history of RA as a progressive and increasingly recalcitrant disease is also well documented. Furthermore, recent studies have shown better outcomes when DMARDs are introduced to naive patients, suggesting that those who have already been exposed to other DMARDs are even more difficult to control. Also, the very nature of the American College of

Rheumatology "response" criteria is such that no absolute value is sought to demonstrate a treatment's success, but rather it is the individual subject's relative improvement compared with his or her baseline assessment. If Dr Smith's assumption was made, this method would also be invalid.

Our design attempted to mimic these criteria in a "real world" situation. Although we agree that some bias was introduced by our design, we would also argue that in order to use subjects as their own controls, their overall status must be the same between the two periods of comparison. Comparing outcomes within the same subject during the first years of a new DMARD would eliminate the presumed problem introduced by Dr Smith's comments, while potentially introducing others.

A more ideal study would be to compare outcomes (that is, flares) between two groups of patients with RA exposed to the same DMARD and matched for multiple variables, including disease duration, number of DMARDs previously used, similar comorbidity, etc. However, this would eliminate the "real world" setting.

Y Yazici, D Erkan, M J Harrison

Division of Rheumatology, The Hospital for Special Surgery, Weill Medical College of Cornell University, New York, USA

Correspondence to: Dr Y Yazici, 515 East 72nd Street, Apartment 18E, New York, NY 10021, USA; yaziciy@hss.edu

CORRECTION

The F158V polymorphism in FcγRIIIA shows disparate associations with rheumatoid arthritis in two genetically distinct populations (Milicic A, Misra R, Agrawal S, Aggarwal A, Brown MA, Wordsworth BP. *Ann Rheum Dis* 2002;61:1021–3.)

There is a discrepancy in the total number of UK patients and controls between the main text (abstract, patients and methods section) and table 1. The correct numbers are as quoted in table 1—that is, UK RA patients (n=401), UK controls (n=420). The numbers of Indian patients and controls are correct.

Corrections printed in the journal also appear on the *Annals* website www.annrheumdis.com and are linked to the original publication.

FORTHCOMING EVENTS**Eleventh Intensive Applied Epidemiology Course for Rheumatologists**

24–28 Feb 2003; ARC Epidemiology Unit, Manchester

No previous experience in epidemiology is required. The course is residential and limited to 25 places

Contact: Ms Lisa Mc Clair, ARC Epidemiology Unit, Manchester, Oxford Road, Manchester M13 9PT, UK

Tel: +44 (0)161 275 5993

Fax: +44 (0)161 275 5043

Email: Lisa@fs1.ser.man.ac.uk

23rd European Workshop for Rheumatology Research

27 Feb–2 Mar 2003; Marseille, France

Contact: Elisabeth Eynier, Secretary, Jean Roudier, Head of Immuno-Rheumatology, INSERM EMI9940, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille CEDEX 5

Tel: +33 4 91 32 44 97

Fax: +33 4 91 83 09 26

Email: elisabeth.eynier@medecine.univ-mrs.fr and jean.roudier@medecine.univ-mrs.fr

Website: www.ewrr.org

Annual European Congress of Rheumatology

18–21 June 2003; Lisbon, Portugal

Contact: Fred Wyss, Executive Secretary EULAR, Witikonstrasse 15, CH-8032, Zurich, Switzerland

Tel: +41 1 383 9690

Fax: +41 1 383 9810

Email: eular@bluewin.ch

Website: www.eular.org

OARS World Congress on Osteoarthritis

12–15 October 2003; Berlin, Germany

Tel: +1 202 367 1177

Fax: +1 202 367 2177

Email: oarsi@oarsi.org

Website: www.oarsi.org

Future EULAR congresses

9–12 June 2004; EULAR 2004 Berlin, Germany

8–11 June 2005; EULAR 2005 Vienna, Austria

21–24 June 2006; EULAR 2006 Amsterdam, The Netherlands