No Significant Sex Differences in Temporal Arteritis

To the Editor:

In recent issues of The Journal, Narvaez, et al and Nir-Paz, et al reported their experience on sex-specific differences in giant cell arteritis (GCA). Narvaez, et al found that among 163 patients with GCA, including 73 with temporal arteritis (TA), the presence of constitutional symptoms was significantly more frequent in women than in men. Women also had a more protracted inflammatory response on laboratory measures. Nir-Paz, et al evaluated 88 patients with either isolated polymyalgia rheumatica (PMR) or TA and found that men and women with GCA differ on their history, presentation, and laboratory findings. Notably, the finding that men are more prone than women to develop irreversible visual ischemia led these investigators to recommend a more aggressive treatment approach to male patients.

These important results compelled us to reexamine the relationship between sex and clinical presentation and prognosis in a large series of patients with TA. Our results, briefly presented below, do not support the difference was not relevant statistically.

In this large homogeneous series of patients with TA, we found only subtle sex-related differences in the clinical presentation at diagnosis, in accord with the results of Narvaez, et al. However, we could not confirm on clinical or laboratory grounds the finding by these investigators of a stronger inflammatory response. The reason men have less specific rheumatic manifestations than women is not known to us, but this observation compares with a male to female ratio of 2 to 3 seen in large series of cases of PMR.

More important, the prognosis for visual manifestations did not appear to be worse in male patients. On the contrary, men more often recalled transient visual ischemic symptoms but less frequently developed permanent visual sequelae, compared with women. We have shown previously that the mean platelet count was the only independent predictor for permanent loss of vision in patients with TA, irrespective of the temporal artery biopsy result. We also noted that patients aged 80 years and older had the worst visual prognosis, particularly bilateral irreversible blindness, but that sex had no influence on visual sequelae. Accordingly, 6 studies totaling more than a thousand patients with TA found no differences in sex distribution in patients with and without permanent visual loss.

Finally, beyond the useful considerations on variants of disease presentation, our study, validated by a large sample size and the fact that patients were treated homogeneously and followed closely, emphasizes that men and women with TA possibly share the same prognosis.

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REFERENCES
To the Editor:

Drs. Nir-Paz and Chajek-Shaul reply

Liozon, et al raise once more the intriguing question of sex differences in giant cell arteritis (GCA). This question has been discussed by us and others in our careful cohort study they show that response to treatment is similar in both men and women, a finding not universally reproduced in other studies. However, are men and women really alike in their expression of GCA, in both the clinical presentation and response to treatment? As reported in several studies, the ratio of women to men with GCA is 2. Other differences are noted as well. Women in the Liozon series tend to have more rheumatic symptoms and occipitalgia, while men have scalp tenderness more commonly. Women are also more severely anemic, a feature reported in other studies. As we reported, some of the main differences between the sexes of our patients were noted in the medical history. Men more often had diabetes mellitus, as well as more frequent cerebrovascular accidents and chronic renal failure. But the overall prevalence of background diseases was the same for both sexes. As described by Duhaut, et al, French patients have a lower incidence of “vasculopathic” comorbidities such as non-insulin-dependent diabetes mellitus. Smoking and previous vascular disease were thought to be associated with GCA in women in this study. This observation gains support from a recent report from Sweden, in which a higher mortality due to vascular diseases was observed, especially in women with GCA.

As reported, men are more prone than women to have visual impairment, a finding not reproduced by Liozon, et al. Moreover, they report a trend for a milder form of blindness in men. In our logistic regression model for predicting blindness we found that the combination of being a male and having a positive GCA pathology was protective against blindness (p < 0.008). As we reported, some of the main differences between the sexes of our patients were noted in the medical history. Men more often had diabetes mellitus, as well as more frequent cerebrovascular accidents and chronic renal failure. But the overall prevalence of background diseases was the same for both sexes. As described by Duhaut, et al, French patients have a lower incidence of “vasculopathic” comorbidities such as non-insulin-dependent diabetes mellitus. Smoking and previous vascular disease were thought to be associated with GCA in women in this study. This observation gains support from a recent report from Sweden, in which a higher mortality due to vascular diseases was observed, especially in women with GCA.
Different populations may have different patterns of sex differences in GCA, while some variables are measured differently in different studies, suggesting differences that may not exist in fact. As we suggested in our study, in order to observe sex differences a comparison to the general population should be performed as well.

Although Liozon, et al did not find major differences between the sexes, they found some evidence to support our previous study. Further population-based studies on an international basis may shed more light on the intriguing question of sex differences in GCA.

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REFERENCES

Dr. Narvaez replies

To the Editor:

I read with interest the letter by Liozon, et al presenting their experience on sex-specific differences in temporal arteritis (TA). They compare their results with the 2 main studies that analyzed this question, including our work1,2.

The main purpose of our report was to draw attention to the possible importance of sex hormones in TA and polymyalgia rheumatica (PMR). Sex differences are known to exist for many autoimmune diseases. The marked female predominance observed in TA and PMR suggests that sex hormones may play a role in etiology and/or disease expression, although the precise significance of this is still not understood because until recently sex-specific differences in both conditions were not extensively explored. We found modest differences in disease expression between women and men. In the 2 conditions, the inflammatory response seemed to be more severe in women, with greater abnormalities in clinical (constitutional syndrome and fever) and laboratory markers of inflammation. No significant differences in the classical features of TA were observed. Although this has not been clearly elucidated before, 2 other reports on TA from Spanish groups also described a strong inflammatory response in women, supporting our results3,4. Whether this strong inflammatory response is related to sex hormones needs further study.
response observed in women implies a lower risk of developing visual loss and other cranial ischemic complications in TA is still controversial, since studies addressing the association between the inflammatory response and the risk of developing irreversible cranial ischemic complications have produced conflicting results6. In this regard, we found no differences in the incidence of visual complications by sex. We hypothesized that the more severe inflammatory response observed in women could explain the longer duration of treatment reported in this subgroup of patients in both PMR and TA, regardless of the treatment regimen6,7. Together, these observations indicate that female patients with these conditions can be at particularly high risk for steroid toxicity, a hypothesis that has been demonstrated in PMR6.

An additional article addressing sex-specific differences in TA and PMR was published later. In this hospital based study of patients from Israel with either isolated PMR or TA, Dr. Nir-Paz and colleagues found that men and women with both conditions differed in their history, presentation, and laboratory findings. One conclusion of these authors is that ophthalmic involvement, specifically blindness, is more common in men. However, these findings have generated controversy, and recently some investigators have questioned the value of this study for making assumptions about sex-dependent disease characteristics of TA due to its methodological limitations4.

Thus the report from Dr. Liozon and colleagues is welcome in order to clarify this issue. Their findings only partially confirm our results, and also reveal subtle sex-related differences in the clinical presentation at diagnosis, without significant differences in the incidence of visual complications by sex. Regarding the laboratory markers of inflammation, they observed lower hemoglobin values in women than in men, without significant sex differences in other measures. Moreover, and contrary to other reports, they did not observe sex differences in the mean duration of treatment or in the incidence of treatment-related side effects. I cannot explain why their results are substantially different in many aspects from previous studies. It seems improbable that these differences can be explained by ethnic differences among different populations, because in another study on TA and PMR from France, Delecoeullerie and colleagues7 found (in contrast to the findings reported by Liozon, et al) that men were more likely to experience visual and other ischemic complications than women, suggesting that “a worse prognosis seems attached to the male sex in TA.” For this reason, the most acceptable hypothesis is that these differences could be related to methodologic differences, including different study designs (prospective versus retrospective studies), selection bias, or the use of specially designed versus standard patient files (the evaluation of clinical findings, when they are mild and do not emerge from a specifically designed study, may have remarkable interobserver variation). In view of these contradictory observations, prospective, multicenter, population based studies will be required to establish universally accepted, clinically relevant conclusions.

While awaiting new data, on the basis of the available studies I feel that sex hormones play a role in the etiology and disease expression of both TA and PMR. This hormonal influence results in a marked female predominance. When they are mild and do not emerge from a specifically designed study, this clinical aspect, women and men seem to have a similar prognosis.

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Disease Modifying Antirheumatic Drugs and Pregnancy

To the Editor:

The article by Dr. Chakravyuty, et al10 points out the need for better data on the use of disease modifying antirheumatic drugs (DMARD) by pregnant women. The article also provides a reminder to rheumatologists about their responsibility to counsel women of childbearing potential regarding potential fetal risks from gestational drug exposures and the need for continued vigilance to prevent pregnancy while taking these drugs. Such counseling may also provide the opportunity to discuss the woman’s interest in future pregnancy and provide preconception counseling regarding the potential complications of her disease for pregnancy including the risk of adverse pregnancy outcome and the potential for worsening of disease with pregnancy. Little is known about the teratogenic potential of most drugs. Misinformation about drug risk in pregnancy is prevalent due to inadequate data collection methodologies. While the authors should be commended for their attempt to provide much needed information, the retrospective collection of human pregnancy outcomes via a survey of physicians represents

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labeling on the use of drugs during pregnancy and is in the process of revis-
working to improve the quantity and quality of data available in product

databases: REPROTEXT, REPROTOX (www.reprotox.org). These periodically updated, scientifically reviewed
resources critically evaluate the literature regarding human and animal

exposed pregnant patients. In addition, the Organization of Teratology

rounds the ascertainment of outcome, including who did the ascertainment
and when it was done. The obstetrician or the rheumatologist may be far
removed from an accurate ascertainment of infant health and mothers may
not be the best source to acquire adequate information regarding congeni-
tal anomalies. Information on live infant outcomes should be obtained from
the infant’s health care provider. Limiting ascertainment of infant outcome
at birth versus at later time in infancy, e.g., at 3 months, will limit the num-
ber and type of major malformations reported. Misclassification of out-
comes may lead to erroneous conclusions.

To proactively encourage the conduct of well designed, scientifically
valid studies in pregnancy, the US Food and Drug Administration (FDA)
recently published a guidance document on establishing pregnancy expo-
sure registries (http://www.fda.gov/cder/guidance/3626fnl.pdf). In these
studies, physicians prospectively enroll their patients after exposure to a
drug during pregnancy but before the outcome of pregnancy is known.
Patients can also self-enroll. These prospective registries offer the opportu-

Unfortunately, the authors missed an excellent opportunity to encour-
age rheumatologists to utilize ongoing epidemiologic studies that collect
information on antirheumatic drug exposure during pregnancy. The manu-
facturer of Arava (leflunomide) is currently enrolling pregnant women
exposed to their drug in such a registry; the labeling, or package insert, for
the product includes a toll-free telephone number for physicians to register
exposed pregnant patients. In addition, the Organization of Teratogenic
Information Services (OTIS) is conducting the Rheumatoid Arthritis and
Pregnancy Study, a prospective study to evaluate risks to the embryo or
fetus with the use of rheumatoid arthritis medications in pregnancy. A list
of pregnancy exposure registries in progress for other drugs is available at
www.fda.gov/womens/registries/default.htm

Current FDA regulations, promulgated in 1979, require prescription
medication labeling to contain a Pregnancy Subsection that includes a
pregnancy letter category (A, B, C, D, or X) that addresses fetal risk of
developmental abnormalities. The FDA recognizes these categories, usu-
ally based only on animal data, can be misleading and that for most prod-

REPROTEXT, REPROTOX (www.reprotox.org), Shepard’s Catalog, and TERIS. These periodically updated, scientifically reviewed
resources critically evaluate the literature regarding human and animal
pregnancy drug exposures. Other sources of information are the more than
20 comprehensive multidisciplinary Teratogen Information Services (TIS)
located in the US and Canada, which provide patient counseling and risk
assessments regarding exposures during pregnancy (www.otispregnan-
cy.org).

With an eye to the future, the FDA Pregnancy Labeling Task Force is
working to improve the quantity and quality of data available in product
labeling on the use of drugs during pregnancy and is in the process of revis-
ings the regulations that govern pregnancy labeling to delete the pregnancy

category scheme and promote the inclusion of more useful clinical infor-
mation in a narrative format.

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University of the Health Sciences, Bethesda, Maryland, USA.

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Dr. Chakravarty, et al, reply

To the Editor:

We read with interest the letter by Dr. Uhl and colleagues in response to our
article about DMARD exposure of pregnant women with rheumatoid
arthritis (RA). We appreciate the interest and discussion raised by our study.

We agree with the points raised by the authors and acknowledge the
limitations inherent in our study. The low response rate is likely, at least in
part, to stem from hesitancy on the part of the physician to disclose infor-
mation about patient outcomes, particularly when they include possible
risks associated with prescribed medications. It is for this reason that we

Unfortunately, there is currently a paucity of published information
about pregnancy outcomes with in utero exposure to these DMARD.
Despite over 2 decades of use of methotrexate in the treatment of RA, there
have been less than 25 reported cases of pregnancy outcomes with gesta-
tional exposure to this agent. The aim of our study was to provide clinicians
with additional information about pregnancy outcomes with exposure to
certain DMARD while we await results from prospective studies. Our
intent was to be descriptive rather than to determine accurate estimates of
risks for adverse pregnancy outcomes. We are concerned about and caution
against misinterpretations of the data to suggest relative risk or safety of
any of these DMARD with respect to gestational exposure.

It is clear that prospectively collected data of pregnancy outcomes of
gestational drug exposure are essential to accurately describe and estimate
risks of adverse events. As described by Dr. Uhl, agencies such as the FDA
and OTIS, as well as industry sponsors, have established such scientifically
valid studies. We encourage all providers and patients to enroll in these
registries once pregnancy with exposure to these medications is discovered.
Unfortunately, the same hesitancy on the part of providers to report preg-
nancies to survey questionnaires may still exist when enrolling patients in
pregnancy exposure registries. These include real or perceived legal, ethi-

cal, and confidentiality issues surrounding potential adverse outcomes to
prescribed medications. There is a need for increased awareness of such registries in order to
enroll the maximum number of exposed pregnancies. We hope that our
study and resulting discussions will encourage increased reporting to vali-
dated pregnancy registries. We applaud the FDA Pregnancy Labeling Task.
Validity of the Scleroderma Functional Assessment Questionnaire

To the Editor:

The Scleroderma Functional Assessment Questionnaire (SFAQ) is a relatively new self-report of functional ability designed specifically for persons with scleroderma. The authors state that the Health Assessment Questionnaire (HAQ)\(^1\), which has traditionally been used to measure function, includes items that are not considered major problems in persons with scleroderma. The 11 item assessment comprises 9 questions regarding upper extremity function and 2 questions regarding muscle weakness. Items are scored on a 4 point scale from 0 (able to perform in a normal manner) to 3 (impossible to perform) and are summed to get a total score ranging from 0 to 33. Kappa scores for test-retest reliability ranged from 0.69 to 0.94, indicating good agreement. Validity was established by comparing subjects’ and therapists’ scores, which yielded kappa scores from 0.19 to 0.60, which constitutes only fair agreement.\(^1\) However, the authors argue that there is no gold standard, as therapists’ perceptions of disability are not more or less valid than subjects’ self-reports. Thus, we compared the SFAQ with performance tests and other self-reports that have been shown to be reliable and valid in persons with scleroderma.

Thirty-four women who fulfilled the American College of Rheumatology criteria for systemic sclerosis (scleroderma)\(^2\) were enlisted as a convenience sample. Ages of participants ranged from 26 to 74 years (mean 53.8 yrs). Disease duration ranged from 3 months to 33 years (mean 10.6 yrs). There were 18 participants with limited scleroderma (ISSc) and 16 with diffuse scleroderma (dSSc). Thirty participants were right handed, while 4 were left handed. Participants were administered these assessments in the following order: the SFAQ, the Hand Functional Disability Scale (HFDS)\(^3\), the Arthritis Hand Function Test (AHFT)\(^4\), the HAQ\(^5\), the Keitel Functional Test (KFT)\(^6\), the Hand Mobility Test in Scleroderma (HAMIS)\(^7\), and skin scores\(^8\). The HFDS is a self-report consisting of 18 items regarding hand ability in 5 categories: kitchen, dressing, hygiene, office, and other. Subjects rate their ability from 0 (no difficulty) to 5 (impossible to do)\(^9\). The AHFT is an 11 item performance-based test that measures grip and pinch strength, dexterity, applied strength and applied dexterity\(^5\). Items are scored on a 4 point scale from 0 (able to perform in a normal manner) to 3 (impossible to perform) and are summed to get a total score ranging from 0 to 21 for each hand. Reliability and concurrent validity have been established for the HFDS (unpublished data), AHFT\(^10\), HAQ\(^11\), and the HAMIS\(^7\) and in persons with scleroderma. Skin thickness of the forearm, hand, and fingers was palpated and rated on a scale from 0 (normal) to 3 (severe skin thickness) to measure disease activity\(^8\).

Table 1 shows descriptive data for the 34 subjects on the SFAQ, HFDS, AHFT, HAQ, KFT, HAMIS, and skin scores. There was no significant difference in scores for any of the variables between the subtypes of scleroderma. Spearman’s rho correlation coefficients were calculated to estimate the concurrent validity of the SFAQ with scores on the HFDS, AHFT,
and Rehabilitation, 1 University of New Mexico, MSC09, Albuquerque, Occupational Therapy Graduate Program, Department of Orthopaedics

Interestingly, while the SFAQ correlated with the AHFT; however, the correlations were weaker. No correlation was found between the SFAQ and skin scores, in agreement with other studies. As well, 3 of the other 2 self-report instruments, as would be expected. As well, 3 of the items on the SFAQ are also on the HAQ and HFDS. Scores also correlated with the AHFT; however, the correlations were weaker. No correlation was found between the SFAQ and skin scores, in agreement with other studies. Yet skin scores have been the traditional outcome used in clinical trials and intervention studies. Interestingly, while the SFAQ correlated with the KFT, the SFAQ did not correlate with the HAMIS. While both of these assessments measure similar joint motions, the KFT consists of 4 items measuring finger flexion, while the HAMIS has only one. However, the HAMIS additionally measures finger extension, and thumb and finger abduction. Perhaps these latter motions are not as important for actual hand function as finger flexion.

In conclusion, clinicians need reliable and valid measures to evaluate the effectiveness of interventions. The SFAQ is simple and quick to administer and has the potential to be useful as an outcome measure of hand function in clinical trials and other intervention studies. The SFAQ is simple and quick to administer and has the potential to be useful as an outcome measure of hand function in clinical trials and other intervention studies.

Table 1. Means and standard deviations for the SFAQ, AHFT, HAQ, HFDS, HAMIS, KFT, and skin scores.

<table>
<thead>
<tr>
<th></th>
<th>dSSc Mean</th>
<th>dSSc SD</th>
<th>ISSc Mean</th>
<th>ISSc SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFAQ</td>
<td>7.0</td>
<td>4.5</td>
<td>6.2</td>
<td>6.7</td>
</tr>
<tr>
<td>HFDS (0–66)</td>
<td>24.3</td>
<td>13.8</td>
<td>20.3</td>
<td>21.1</td>
</tr>
<tr>
<td>AHFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength total, pounds</td>
<td>122.0</td>
<td>39.0</td>
<td>129.2</td>
<td>43.8</td>
</tr>
<tr>
<td>Dexterity total, s</td>
<td>51.1</td>
<td>11.2</td>
<td>49.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Applied dexterity, s</td>
<td>161.5</td>
<td>52.6</td>
<td>145.5</td>
<td>54.4</td>
</tr>
<tr>
<td>Applied strength, mm</td>
<td>4905.1</td>
<td>1184.3</td>
<td>4815.3</td>
<td>1326.3</td>
</tr>
<tr>
<td>HAQ (0–5)</td>
<td>1.1</td>
<td>0.5</td>
<td>1.1</td>
<td>0.75</td>
</tr>
<tr>
<td>KFT (0–42)</td>
<td>17.6</td>
<td>12.4</td>
<td>13.6</td>
<td>9.3</td>
</tr>
<tr>
<td>HAMIS (0–54)</td>
<td>12.2</td>
<td>10.4</td>
<td>6.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Skin score total (0–18)</td>
<td>25.2</td>
<td>15.1</td>
<td>19.8</td>
<td>13.9</td>
</tr>
</tbody>
</table>

AHFT: Arthritis Hand Function Test; HAMIS: Hand Mobility Test in Scleroderma; KFT: Keitel Functional Test; HAQ: Health Assessment Questionnaire; HFDS: Hand Function Disability Scale.

Table 2. Relationships between the SFAQ, performance measures of hand function, and other self-reports.

<table>
<thead>
<tr>
<th></th>
<th>Spearman rs</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFDS</td>
<td>0.84</td>
<td>0.0001</td>
</tr>
<tr>
<td>AHFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength total, pounds</td>
<td>−0.50</td>
<td>0.01</td>
</tr>
<tr>
<td>Dexterity total, s</td>
<td>0.36</td>
<td>0.05</td>
</tr>
<tr>
<td>Applied dexterity, s</td>
<td>0.35</td>
<td>0.05</td>
</tr>
<tr>
<td>Applied strength, mm</td>
<td>−0.62</td>
<td>0.0001</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.76</td>
<td>0.0001</td>
</tr>
<tr>
<td>KFT</td>
<td>0.39</td>
<td>0.05</td>
</tr>
<tr>
<td>HAMIS</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Skin score total</td>
<td>0.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

HAQ, KFT, HAMIS, and skin scores. Table 2 shows the SFAQ correlated significantly with the HFDS, AHFT, HAQ, and the KFT.

Our results support the use of a self-report questionnaire, the SFAQ, with persons who have scleroderma. The study provides further support for the concurrent validity of the SFAQ. The SFAQ correlated strongly with the other 2 self-report instruments, as would be expected. As well, 3 of the items on the SFAQ are also on the HAQ and HFDS. Scores also correlated with the AHFT; however, the correlations were weaker. No correlation was found between the SFAQ and skin scores, in agreement with other studies. Yet skin scores have been the traditional outcome used in clinical trials and intervention studies. Interestingly, while the SFAQ correlated with the KFT, the SFAQ did not correlate with the HAMIS. While both of these assessments measure similar joint motions, the KFT consists of 4 items measuring finger flexion, while the HAMIS has only one. However, the HAMIS additionally measures finger extension, and thumb and finger abduction. Perhaps these latter motions are not as important for actual hand function as finger flexion.

In conclusion, clinicians need reliable and valid measures to evaluate the effectiveness of interventions. The SFAQ is simple and quick to administer and has the potential to be useful as an outcome measure of hand function in clinical trials and other intervention studies.

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REFERENCES
ICAM-1 gene polymorphisms have been reported to be important candidate susceptibility factors for multifactorial diseases with an inflammatory component. Given the inflammatory effect of EN, we assessed the implication of ICAM-1 polymorphisms in this condition.

All patients (n = 101, ages 15–78 yrs) in our study were diagnosed with biopsy-proven EN in close collaboration between the rheumatology and dermatology divisions of the Hospital Xeral-Calde in Lugo, Spain. Thirty-six were diagnosed as having idiopathic EN and the remaining 65 as secondary EN (31 of them had EN in the setting of sarcoidosis). Controls (n = 129) were also from Lugo.

DNA from patients and controls was extracted from anticoagulated blood collected in EDTA using a commercial DNA extraction kit (Bioline®, London, UK).

Molecular analysis of ICAM-1: as reported, amino acid polymorphisms, substitution of R for G at codon 241, and substitution of K for E at codon 469 were examined by polymerase chain reaction restriction fragment length polymorphism.

Associations between patient groups and controls and alleles or genotypes of ICAM-1 polymorphisms were estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined as p < 0.05. Power calculation was performed for an unmatched case-control study and estimated relative risk using EpiInfo 2000, v. 1.1.2 software.

We found that in the control group, allele and genotype frequencies for ICAM-1 polymorphisms were in Hardy-Weinberg equilibrium; the chi-square data for the observed versus estimated expected genotype for ICAM-1 codon 241 and codon 469 in the control group were 1.9, p = 0.3, and 0.9, p = 0.6, respectively.

No differences between the whole group of patients with biopsy-proven EN and controls were observed for either polymorphism. This was also the result when patients with idiopathic and secondary EN were compared (Table 1). Similarly, no differences between patients with EN associated with sarcoidosis and the remaining group of EN secondary to other etiologies were found (Table 2). A small increase was observed in the frequency of R/G heterozygous for ICAM-1 (241 R/G) polymorphism in patients with EN associated with sarcoidosis compared to the controls (23% versus 13%) (p = 0.2, OR 1.9, 95% CI 0.7–5.1). Given the sample sizes and the allele frequencies of these polymorphisms, we can exclude with 80% certainty a genetic relative risk of 2.7 for ICAM-1 polymorphism at codon 241 and a genetic relative risk of 3.0 at codon 469 for sarcoidosis in Lugo.

ICAM-1 polymorphisms have been investigated in several diseases where diverse genetic and environmental factors are implicated in the development of an inflammatory response. Patients with ulcerative colitis who were antinuclear cytoplasmic antibody-negative had a significantly increased frequency of allele R241 compared with antibody-positive patients. In patients with multiple sclerosis a significantly higher frequency of the exon 6 homozygote K469 genotype was found compared to controls. This was independent of the association attributed to HLA-DR2. In renal transplant recipients allograft failure was associated with R at codon 241, and a more rapid failure of the allograft in the presence of E at codon 469 was also found. ICAM-1 gene polymorphisms have also been implicated in the pathogenesis of some systemic vasculitides such as in Behçet’s disease and giant cell arteritis.

Our analysis constitutes the first attempt to assess the influence of ICAM-1 polymorphisms in a large series of biopsy-proven EN. Given the sample sizes and the allele frequencies of these polymorphisms, we can exclude a genetic relative risk of those ICAM-1 polymorphisms for EN in Northwest Spain. However, interpretation of these results could to some extent be limited because EN is a very heterogeneous entity.

| Table 1. Allele and genotype frequencies of ICAM-1 gene polymorphisms in biopsy-proven erythema nodosum (EN) and controls*. |
|---|---|---|---|---|
| Gene | Controls | EN (total) | Idiopathic | Secondary |
| **ICAM-1 (codon 241)** | | | | |
| Genotype | n = 129 (%) | n = 101 (%) | n = 36 (%) | n = 65 (%) |
| **RR** | 2 (2) | 0 (0) | 0 (0) | 0 (0) |
| **RG** | 17 (13) | 20 (20) | 6 (17) | 13 (20) |
| **GG** | 110 (85) | 81 (80) | 30 (83) | 52 (80) |
| **Allele** | | | | |
| **R** | 21 (8) | 20 (10) | 6 (8) | 13 (10) |
| **G** | 237 (92) | 182 (90) | 66 (92) | 117 (90) |
| **ICAM-1 (codon 469)** | | | | |
| Genotype | n = 117 (%) | n = 98 (%) | n = 34 (%) | n = 64 (%) |
| **KK** | 28 (24) | 24 (25) | 9 (26.5) | 15 (23) |
| **KE** | 67 (57) | 52 (53) | 16 (47) | 36 (56) |
| **EE** | 22 (19) | 22 (22) | 9 (26.5) | 13 (20) |
| **Allele** | | | | |
| **K** | 123 (53) | 100 (50) | 34 (50) | 66 (52) |
| **E** | 111 (47) | 96 (50) | 34 (50) | 62 (48) |

* No statistically significant differences were observed.

REFERENCES
Table 2. Allele and genotype frequencies for ICAM-1 polymorphisms in patients with EN secondary to sarcoidosis and those due to other etiologies*.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Controls</th>
<th>EN Secondary to Sarcoidosis</th>
<th>EN Secondary to Other Etiologies</th>
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<tr>
<td>ICAM-1 (codon 241)</td>
<td>n = 129 (%)</td>
<td>n = 31 (%)</td>
<td>n = 34 (%)</td>
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<td>Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RG</td>
<td>17 (13)†</td>
<td>7 (23)†</td>
<td>6 (18)</td>
</tr>
<tr>
<td>GG</td>
<td>110 (85)</td>
<td>24 (77)</td>
<td>28 (82)</td>
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<tr>
<td>R</td>
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<td>7 (11)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>G</td>
<td>237 (92)</td>
<td>55 (89)</td>
<td>62 (91)</td>
</tr>
<tr>
<td>ICAM-1 (codon 469)</td>
<td>n = 117 (%)</td>
<td>n = 31 (%)</td>
<td>n = 33 (%)</td>
</tr>
<tr>
<td>Genotype</td>
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</tr>
<tr>
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<td>9 (29)</td>
<td>6 (18)</td>
</tr>
<tr>
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<td>19 (58)</td>
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<tr>
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<tr>
<td>E</td>
<td>111 (47)</td>
<td>27 (44)</td>
<td>35 (53)</td>
</tr>
</tbody>
</table>

* No statistically significant differences were observed. † p = 0.2, OR 1.9, 95% CI 0.7–5.1.

Correction


Signatures for the letter should include the third author, Peter Jacobs, BM, BCh, MD, PhD, The Department of Haematology and Bone Marrow Transplantation Unit, Constantiaberg Medi Clinic, Cape Town, South Africa. We regret the error.