Economic cost and epidemiological characteristics of fibromyalgia.

John Quintner and Milton Cohen

J Rheumatol 2004;31;2311
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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Low Sensitivity of Anti-α-Fodrin Antibodies in Patients with Primary Sjögren’s Syndrome

To the Editor:

We read with interest the article by Witte, et al relating to the prevalence of anti-α-fodrin antibodies in patients with primary Sjögren’s syndrome (pSS). They found greater diagnostic sensitivity in patients classified according to the San Diego criteria (88% IgA, 64% IgG) than in those classified on the basis of the criteria proposed by the European Community Study Group (63% IgA, 49% IgG). According to Witte, et al, application of the European classification criteria, which do not necessarily require a biopsy of the minor salivary glands, involves the risks of including patients with sicca syndrome but not SS. Conversely, using the more restrictive US criteria, which require a positive histological examination, the classification of pSS would be more accurate, and in this case, the overall positivity of the anti-α-fodrin antibodies (IgA and IgG) would be in excess of 90%.

We studied 174 patients with pSS to evaluate the sensitivity of the test for anti-α-fodrin antibodies, 141 patients with other connective tissue disorders or viral infections, and 40 healthy subjects to evaluate its specificity. Of 174 patients with pSS, the disorder was classified according to the European Community criteria in a subgroup of 123 patients, and according to the US criteria in a subgroup of 51 patients. Anti-α-fodrin antibodies of class IgA and IgG were studied in parallel with 2 solid-phase immunoenzymatic methods, with kits from Aesku.lab Diagnostika (Wandelsheim, Germany) and Orgentec Diagnostika (Mainz, Germany). Both tests were performed according to the manufacturer’s instructions, using the cutoffs recommended by each.

The overall sensitivity of the test for antibodies of class IgA and IgG was 22.9% and 15.5%, respectively, for the Aesku.lab method and 19.8% and 12.7% for the Orgentec method. In the subgroup of 51 patients whose diagnosis included a positive biopsy among the classification criteria, the sensitivity for IgA and IgG was 17.6% and 9.8% for Aesku.lab, and 13.7% and 11.8% for Orgentec. The specificity was 91.5% for the Aesku.lab method and 90% for the Orgentec method. The global agreement (positives/negatives) between the 2 methods was 73% for IgA and 72% for IgG, but much lower (20% IgA, 3% IgG) for positive cases only (Table 1). It is noteworthy that, while only 7% of patients were recognized as IgA positive and 1% IgG positive by both methods, positive cases of either of the 2 methods were 34% for IgA and 29% for IgG, showing that the 2 tests identified 2 different anti-α-fodrin positive pSS populations. The percentage of positivity for other antibodies was as follows: antinuclear antibodies 97.1% (by indirect immunofluorescence; Inova, San Diego, CA, USA); anti-Ro, 86.8%; anti-La, 43.8% (ELISA; Diasorin, Saluggia, Italy). None of the 3 antibodies proved to correlate with an-α-fodrin IgA or IgG.

Thus, our findings do not confirm those obtained by Witte, et al. On the contrary, the results in our group of patients with pSS confirmed by biopsy were actually worse in terms of sensitivity. There is no clear explanation for this great discrepancy. However, our results confirm those obtained by other researchers, showing that in general the good specificity value of anti-α-fodrin antibodies is not matched by acceptable sensitivity. This finding may be due to low nosographic sensitivity (in the case of the anti-Sm antibodies in systemic lupus erythematosus or anti-synthetases in polymyositis), or to the fact that the current antigen formulations do not have all the relevant epitopes (low analytical sensitivity). In view of the low agreement between the 2 methods used, the second hypothesis is more probable, and it will be necessary to await the introduction of second-generation methods in order to evaluate the efficacy of this new antibody measure in the laboratory diagnosis of SS.

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REFERENCES


Table 1. Percentage distribution of IgG anti-α-fodrin results achieved by the 2 kits employed, in 174 patients with Sjögren’s syndrome.

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<th>Aesku.lab</th>
<th>Orgentec</th>
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<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>IgA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neg</td>
<td>17</td>
<td>71</td>
</tr>
<tr>
<td>Pos</td>
<td>7</td>
<td>12</td>
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Table 1 shows the percentage distribution of IgG anti-α-fodrin results achieved by the 2 kits employed, in 174 patients with Sjögren’s syndrome.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 4 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. The Managing Editor, The Journal of Rheumatology, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.
In order to determine the role of antibodies against α-fodrin in Sjögren’s syndrome (SS), we deliberately collaborated with a number of groups. In those studies with carefully selected, untreated patients, the prevalence of antibodies against α-fodrin in SS was 77% in patients from Freiburg, 55% in patients from Munich, and 72% in our own patients. In another independent blinded study, the prevalence was 70% in patients from Lille, France. However, a few other groups, including Dr. Bizzaro and colleagues, have reported a lower prevalence of antibodies against α-fodrin. In many cases, the differences can be explained by a less than optimal selection of patients, in whom sicca syndrome had not been clearly differentiated from SS.

In the study from Bizzaro, et al., patients apparently were carefully selected, but still there remain 2 problems: (1) In the studies of our colleagues from Israel, the concentration of antibodies against α-fodrin correlated with the lymphocytic infiltration in the salivary glands and appears to reflect disease activity. According to our own observations, the prevalence of antibodies against α-fodrin normalizes 4–8 weeks after treatment with antimalarials, low dose corticosteroids, or immunosuppressives has been started. Low prevalences of antibodies against α-fodrin have therefore been observed by colleagues who tend to treat SS with these drugs. Optimally, the prevalence of antibodies against α-fodrin has to be studied in untreated patients, as we have done. (2) At the time, when we used Aesku.lab ELISA kits for our studies, the plates were used very soon after production. According to information from Aesku.lab, Dr. Bizzaro tested the Aesku.lab kit as one of the first after larger production of ELISA plates had started, and the plates were stored for a longer period. However, it turned out that α-fodrin was an extremely unstable protein and that several epitopes tended to degrade even when the protein was coupled to the plates. Therefore, although the controls directed against epitopes that were not affected looked fine, many sera that had been positive before lost activity. That also explains the low sensitivity reported by Sibilia, et al., who tested the kit at the same time as Bizzaro. The problem with the stability of α-fodrin had been fixed shortly after Bizzaro had tested the assay, and we have not had problems even after introducing the test into our routine laboratory diagnostics.

Even though we think that the results described by Bizzaro, et al will be similar to our own studies, when the test is repeated on untreated patients only, their comments exemplify problems in diagnostic procedures for SS. If classification criteria are used uniformly, the prevalence of diagnostic markers should be comparable in all studies. Therefore, as we wanted to assert in our study, the true association of markers with Sjögren’s syndrome will only be determined when genetic risk markers have been identified.

Dr. Dobkin replies

To the Editor:

I wish to apologize to your correspondents, Drs. Quintner and Cohen, if I have inadvertently misquoted them in my correspondence with the Editor.
Although the majority of patients with PsA run a benign course, in 20% a chronic progressive deformating arthritis may develop. A characteristic finding is enthesopathy, which is said to be common. Enthesopathy may occur in the absence of other joint symptoms and is poorly recognized in previous studies on PsA. It has been estimated to have a prevalence as high as 38%. SSZ is often used in PsA and has been found to be safe, well tolerated, and effective.

We assessed the effect of SSZ in the treatment of enthesitis in patients with PsA, using the Newcastle Enthesis Index (EI), Disease Activity Score 28 (DAS-28), and Health Assessment Questionnaire (HAQ), with improvement in these 3 scores as the primary outcome measure.

We performed an open study; patients invited to take part were older than 16 years, had PsA and enthesitis as defined by EI with a score ≥ 1, and had psoriatic skin lesions or nail changes. Standard dosages of SSZ were used. Exclusions were oral steroids or other concurrent disease modifying antirheumatic drug. Patients were assessed within 4 weeks of commencing SSZ treatment, and at 3 and 6 months after treatment began. At each visit the EI, DAS-28, and HAQ were assessed.

Over a period of 22 months 26 consecutive patients with PsA and enthesitis were identified. Four declined SSZ treatment after discussion regarding the use and monitoring of the drug. Of the remaining 22, two were not able to be assessed within 4 weeks of starting treatment due to difficulties in arranging an appointment. Twenty began SSZ and had a baseline assessment. One continued SSZ but did not respond to contact for further participation in the study. Two patients could not attend for monitoring due to work reasons; the drug was therefore discontinued by the patient (both men). Nine discontinued treatment (7 women, 2 men). Reasons for discontinuation included gastrointestinal side effects (n = 4), headaches (n = 1), dyspepsia + rash (n = 1), and other side effects (n = 1). Ten patients completed 6 months of SSZ (6 women, 4 men).

Of the 20 patients assessed at baseline there were 13 women and 7 men. Their mean age was 49 years and the erythrocyte sedimentation rate (ESR) at baseline was 10.2 mm/h (range 1–48). Mean HAQ was 1.656 (range 0.125–3), mean DAS-28 4.146 (range 1.22–6.29), and EI 21.35 (range 8.5–48). Eight patients had PsA and enthesitis and for others that I would like to discuss.

Table 1. Outcomes of study completers. Values are mean (range).

<table>
<thead>
<tr>
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<th>Month 0</th>
<th>Month 3</th>
<th>Month 6</th>
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<tbody>
<tr>
<td>ESR, mm/h</td>
<td>6.5 (2–11)</td>
<td>6.1 (2–15)</td>
<td>5 (1–10)</td>
</tr>
<tr>
<td>CRP, g/l</td>
<td>7.33 (&lt; 5–10)</td>
<td>8.4 (&lt; 5–10)</td>
<td>6 (&lt; 5–6)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.5875 (0.125–2.875)</td>
<td>1.7 (0–2.75)</td>
<td>1.486 (0–2.875)</td>
</tr>
<tr>
<td>DAS</td>
<td>3.7 (1.22–6.29)</td>
<td>3.11 (1.6–6.6)</td>
<td>3.39 (1.06–5.74)</td>
</tr>
<tr>
<td>Enthesitis Index</td>
<td>21 (1–50)</td>
<td>17 (1–43)</td>
<td>15 (2–43)</td>
</tr>
</tbody>
</table>

Although overall trends of improvement were observed in all assessments, these results did not reach statistical significance. Similar trends were found in patients’ own assessment of pain and physicians’ global assessment. There were no significant differences in baseline characteristics between the responders and nonresponders.

We also found no significant improvement in any outcome measure used; however, our numbers are small. We had a high dropout rate due to inconvenience of taking the drug and subsequent monitoring, and also a high incidence of side effects: 7/24 (29%) of our study patients withdrew because of these, compared to 8/20 (40%) in the van Denderen, et al study. However, the HAQ scores show a level of disability and DAS-28 scores a level of disease activity that suggest this group of patients should receive treatment. ESR does not reflect disease in these patients.

We found results using aminosalicylates in this seronegative arthritis group were similar to those of van Denderen, et al in AS.

A more effective and better tolerated treatment for psoriatic enthesitis is needed.

REFERENCES


Dr. van der Horst-Bruinsma replies

To the Editor:

On behalf of my co-authors I would like to thank Dr. Kumar, et al for referring to our article and for their execution of a more or less comparable study. However, there are some main differences between their study and ours that I would like to discuss.

First of all, the patients included in our study were diagnosed as ankylosing spondylitis (AS) according to the modified New York criteria and had no other forms of spondylarthropathy (SpA), such as psoriatic arthritis. Moreover, our focus was not directed to the decrease of enthesitis or arthritis, but to other outcome measures such as the Bath Ankylosing Spondylitis Disease, Functional, and Metrology indexes.

The only corresponding outcome variable shared by both studies is the erythrocyte sedimentation rate (ESR), which decreased in our study, but remained the same in the 10 patients that completed the 6-month followup period.

Another discrepancy is the choice of the drug: mesalazine (Salofalk®) used in our study is not the same compound as sulfasalazine (SSZ), which is supposed to cause more gastrointestinal side effects than other sulfa preparations. Mesalazine is not commonly used in AS or SpA, whereas for years SSZ has been considered an effective therapy in rheumatoid arthritis, psoriatic arthritis, AS, and SpA.

Studies on SpA show an efficacy of SSZ in improvement of the ESR and peripheral arthritis, but not in spinal mobility, morning stiffness, or other disease activity scores. Table 1 of Kumar, et al shows a small, but insignificant, improvement in the Disease Activity Score. This might be
due to an improvement of the joint score, since the ESR remained constant. It would be interesting to give the swollen and tender joint count as a separate outcome measure.

The main observation in their study, that the enthesitis index does not improve with SSZ, is not surprising, taking into account the therapy-resistant course of enthesitis. Treatment with tumor necrosis factor-blocking agents would probably be more effective.

The high number of side effects of SSZ is unexpected. This might be due to the dosage, slow increase in the starting dose, and the sort of tablets used (enteric-coated or not). It would be interesting to learn of these aspects, as in many studies with SpA, a relatively high dose of 3 g daily was used.

The last point I would like to bring up is the high number of noncompleters (50%). Perhaps the results might change if an intention-to-treat analysis is performed.

In conclusion, I think it is interesting to study whether enthesitis can be influenced by DMARD therapy. However, the disappointing results might be due to the therapy-resistant outcome measure that was chosen, namely enthesitis. Perhaps an intention-to-treat analysis would result in more positive results.

IRENE E. van der HORST-BRUINSMA, MD, PhD, Rheumatologist, VU University Medical Centre, Amsterdam, The Netherlands.

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**Letters**

Magnetic Resonance Imaging and 31P Magnetic Resonance Spectroscopy Investigations of Muscle Function Disclose No Abnormality in Macrophagic Myositis

To the Editor:

Macrophagic myositis (MMF) has been recently described as a localized inflammatory muscle disease on the basis of histological investigations. MMF might be triggered by aluminum hydroxide used as adjuvant in hepatitis A, hepatitis B, and tetanus toxoid vaccines in order to enhance anti-vaccine antigen immune responses. Muscle biopsy performed on the vaccination site typically shows infiltration of connective tissue by large, CD68+ macrophages1. Various clinical symptoms such as diffuse myalgia, arthralgia, marked asthenia, muscle weakness, fever, and symptomatologic demyelinating central nervous system disorder have been reported to date, while no clear link has been established with myositis2-4. Although it has been suggested that aluminum hydroxide-containing vaccine might account for histological changes of MMF in the context of the HLA-DRB1*01 genetic background5, a link between aluminum hydroxide injections and clinical symptoms has not been established. Considering the skeletal muscle signs, the existence of an underlying or vaccine-induced myopathy could be suspected, but no data regarding muscle function have been available to date. We investigated whether muscle energy metabolism and muscle anatomy are altered in patients with MMF similarly to what has been observed in other inflammatory diseases6-8.

Nine patients with MMF (7 men, 2 women, mean age 40.7 ± 8.7 yrs) were studied, and the diagnosis of MMF was performed according to histopathological results. Using 31P magnetic resonance spectroscopy (MRS), high-energy phosphate compound concentrations and pH values were recorded throughout a rest-exercise-recovery protocol as described9. Control subjects (n = 27, 12 women) were free from chronic or acute muscle disease. Conventional magnetic resonance imaging (MRI) sequences (T1 and T2 weighted and inversion-recovery techniques) were performed on thigh muscles. The statistical distribution of sex and age was similar in the 2 groups.

In all patients, inflammatory infiltrates containing macrophages were observed within muscle and fascia. Intracytoplasmic spiculated inclusions were detected by electron microscopy. Two clinical patterns were observed in the patient group, i.e., central and/or peripheral nervous system involvement in 4 patients and myalgias and chronic fatigue in the remaining 5. In the latter group, no particular MRI abnormality was observed, whereas in the former group signs of muscle atrophy with fatty infiltration were found (Figure 1). At rest, the ratios of metabolite concentrations (PCr/ATP, Pi/ATP, and PCr/Pi) and pH values were not different between groups. Accordingly, as shown in Figure 2, the average absolute PCr concentration measured at rest was similar in both groups (33.4 ± 4.5 mM in the MMF group vs 34.3 ± 3.1 mM in controls), while the scattering of data was also identical. Exercise-induced PCr and pH changes were of similar magnitude in both groups. As expected, muscle contraction led to PCR consumption (17.9 ± 7.1 mM in MMF patients vs 23.8 ± 10 mM in controls) and intracellular acidosis (0.41 ± 0.26 pH unit in MMF patients vs 0.50 ± 0.22 pH unit in controls). In the early period of exercise, intracellular alkalosis was recorded as a result of H+ consumption through PCr breakdown. Thereafter, pH decreased, indicating a net H+ production related to anaerobic glycogenolysis coupled to ATP hydrolysis10. Accumulation of ADP (calculated from PCr and pH changes) was similar in both groups. The initial rate of PCr recovery did not differ between groups, indicating, when taking account of end-exercise ADP values, normal involvement of aerobic ATP production in patients.

In light of these results, an impairment of muscle energy metabolism could clearly be ruled out in patients with MMF. Oxidative and anaerobic energy production during exercise was similar in MMF patients and controls. This is in contrast to the increased energy cost previously reported in dermatomyositis, thereby excluding such a myopathy or even a glycogenolytic disorder as a cause of myalgias in MMF11. Regarding a potential oxidative disorder, the rate of PCr changes in the initial recovery period provides unquestionable evidence of normal aerobic function, thereby excluding a mitochondrial impairment in MMF patients12. Considering the MRI results, the signs of atrophy and fatty infiltration observed in patients with neurological symptoms are very common and are nonspecific for a particular neuromuscular disease. They might only reflect a deconditioning phenomenon due to reduced physical activity13. Apart from a metabolic muscle disorder, other physiopathological hypotheses have been put forth, considering MMF either as a fortuitous association with other connective tissue disorders or as a new clinical syndrome related to a chronic immune response induced by aluminum granulomas persisting at the sites of prior immunization14. The existence of a genetic predisposition has also been described15, and all these issues will be more precisely documented in the future.

It can be concluded from our study combining 31P MRS and MRI that neither alterations of mitochondrial function nor modifications in glycolytic or glycogenolytic pathways can account for muscle signs in patients with MMF, indicating that no primary or secondary underlying anomaly of muscle energy metabolism is responsible for the observed clinical symptoms.

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Figure 1. Axial T1 weighted spin echo (A) and axial turbo spin-echo STIR MR images (B) recorded in a patient (complaining of myalgia) and showing normal appearance of the thigh muscles with no evidence of edema, fatty infiltration, or atrophy. Axial T1 weighted spin-echo (C) and axial turbo spin-echo STIR MR images (D) recorded in another patient (with muscle weakness, amyotrophy, and pyramidal syndrome of the 4 limbs) showing clear diffuse muscle atrophy with fatty infiltration.

Figure 2. Scattergram of PCr concentrations at rest measured in both study groups. Average values in each group are shown with error bars representing SD.
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Book Review


This third edition of the textbook Rheumatology continues to be a most valuable and definitive text for rheumatologists and rheumatology trainees. In its expansive 2364 pages, in 17 well laid out sections, this text has improved over the last edition in terms of organization and content. Something as simple as the change to ordinal numbers has made it easy to index and find the area of interest to the reader. The size of the lettering in the index, however, requires bifocals and a magnifying glass for those of us over fifty. The sections are more cohesive; an example is the section on regional and widespread pain, which is a result of amalgamating 3 sections from the last edition. Practical problems have in this way been eliminated and appropriately incorporated throughout the text. The chapters are edited and presented with clarity. The text, photographic and x-ray images, tables, and algorithms continue to be of outstanding quality. For those who prefer it, the CD-ROM is an added benefit.

In terms of content, there is increased emphasis on the history of rheumatic disorders, epidemiological concepts, principles of health outcomes and economics, newer classification of rheumatic disorders, imaging techniques, and the scientific basis of rheumatic disorders. This text is detailed and comprehensive, and covers the gamut of rheumatology including recent advances in genetics, immunology, tissue destruction and repair, and inflammation. The text also includes reference to the expanding role of rehabilitation medicine and the interdisciplinary care of the patient with arthritis. In particular, the therapeutic sections of rheumatoid arthritis and juvenile idiopathic arthritis have been revamped to reflect the newer immunotherapies in practice, as well as emerging new therapies.

This textbook is a must for libraries, academic clinicians, educators, and students of rheumatology. As with any text, the references and material reflect the date of publication and no doubt a fourth edition will soon be a work in progress.

Rachel Shupak, MD, FRCPC. St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada

Correction

Furst DE. Window of opportunity [editorial]. J Rheumatol 2004;31:1677-9. The first paragraphs, page 1677, should appear as follows:
“...In this analogy, our present-day medications would not be as effective given later as given early; this time period of greatest effectiveness is the window of opportunity. And when considering the opening of a window of opportunity, one must also consider the concept of closing such a window.

First, do the data demonstrate that treating at an early point after RA begins is more effective than treating later?...”

Within paragraph 3 on page 1677, at line 10, the text should read as follows:
“...Borg, et al, in a double-blind, randomized study, treated patients with < 2 years’ disease with auranofin or placebo and followed patients for 24 months. An average 8 month delay in starting auranofin was still discernible as more [not less] joint swelling and more [not less] radiographic progression at 24 months.”

We regret the errors.