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***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.**

Origins of Erosive Arthritis

To the Editor:

We read with great interest the article by Rothschild, *et al*, entitled "Unified Theory of the Origins of Erosive Arthritis: Conditioning as a Protective/Directing Mechanism"[1]. Rothschild and colleagues point out (1) a potential relationship between the presence of tuberculosis (TB), considered universal as a *gibbus* phenomenon (destruction of posterior vertebral elements) is present in 1–2% of the population, and spondyloarthritis; and (2) an absence of geographic and time concurrence of TB and rheumatoid arthritis (RA). We consider his theories intuitive and innovative. We would like to offer some observations from our experience, which we would be most pleased to be explained by Dr. Rothschild.

Some authors have reported that TB is not increased in patients with RA compared to the general population or to other rheumatic diseases[2,3], a finding that would support Rothschild, *et al*. Neither our group nor others have observed this, however[4,5]. The results of the largest study saying that TB is not increased in patients with RA, Wolfe, *et al* in United States[2], are inconclusive, as the confidence interval covers all results from a lower rate than in the general population to a much higher rate. In the EMECAR study[5], which we carried out in Spain, a setting with a greater rate of TB compared to United States (25 vs 6.2 per 100,000), the confidence interval is much narrower than in Wolfe's study and therefore, the information is more precise and clear: TB is increased 4-fold in patients with RA. Further, this increase is not so clearly related to the use of specific drugs, as McGrath recently pointed out in a letter[6], although it may have to do with immunosuppression from multiple causes. TB cases in the EMECAR study had not been previously exposed to the new anti-tumor necrosis factor drugs, which have clearly showed an association with increased rate of TB[7]. Rothschild recommends a review of the cases of RA with TB, in case they were a peripheral form of a spondyloarthritis. We have reviewed all cases of patients with RA with TB in the EMECAR and in the BIOBADASER study, a national registry of adverse events in rheumatic diseases treated with biologics, and all of them fulfill the American College of Rheumatology criteria[8] and lack sacroiliitis.

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Dr. Rothschild replies

To the Editor:

The crux of the question raised by Dr. Juan-Mas and Dr. Carmona is the definition of rheumatoid arthritis (RA). While fulfillment of the American College of Rheumatology (ACR) criteria and lack of sacroiliitis may be sufficient for entry of patients into drug studies, it is not adequate for distinguishing RA from spondyloarthropathy (SpA). Even individuals with psoriasis frequently fulfill the ACR criteria, especially with the deletion of the original "exceptions" category[1,2].

Demonstrated (exclusive of the sacroiliac joint) distinguishing skeletal features of SpA include subchondral localization of erosions, para-erosional new bone formation, preservation of residual para-erosional trabeculae, enthesial calcification, zygapophyseal joint fusion and erosions, costovertebral joint fusion and erosions, syndesmophytes, erosion of anterior-superior and anterior-inferior vertebral margins, often more limited distribution (fewer joints than in RA, even in those with polyarticular disease), and presence of characteristic patterns (including arthritis mutilans, all joints on a single digit, and distal interphalangeal joint predominant)[3-10].

The most likely consideration is problems in recognition of the polyarticular presentation of SpA[4,5]. While diagnosis of SpA is facilitated in the presence of sacroiliac joint erosion or fusion, that is only found in less than half of individuals with SpA[3-5,8]. Recognition of SpA in the latter group and distinguishing it from other erosive disorders, such as RA, is the challenge, I suspect, in EMECAR cases.

Juan-Mas and Carmona report that their clinical experience mimics mine. It is the drug study patients that require clarification. A "broad definition" of RA may relate to the "lumper-splitter" issue[8,9]. I certainly would appreciate an opportunity to examine the radiographs and case histories in the EMECAR and BIOBADASER studies with Juan-Mas and Carmona, as only through such collaborative efforts can this question be clarified.

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Interferon-α (IFN-α) Application Versus Tumor Necrosis Factor-a Antagonism for Ocular Behçet's Disease: Focusing More on IFN

To the Editor:

We read with interest the article by Ohno, *et al*[1], on the efficacy of infliximab in 13 patients with Behçet's disease (BD) and refractory uveitis and the corresponding editorial by Rosenbaum[2] in the same issue.

Ohno, *et al* present the first open label trial in a "larger" group of patients with BD and cyclosporin A (CSA) and glucocorticoid resistant uveoretinitis. There have been case reports on infliximab for this indication before[2-5]. The number of ocular attacks decreased significantly during the 51-day (median) observation period.

However, some points must be addressed: The dosage chosen (5 mg and 10 mg/kg body weight) was high (standard dosage for rheumatoid arthritis would be 3 mg/kg bw) and hence treatment becomes very expensive. Neutralizing anti-mouse-antibodies were measured positive in 7 patients; these probably will develop in a relatively high number of patients considering the high dosages given.

Adverse events were quite common, about one-third of patients experienced diarrhea, cold, nausea or vomiting, and changes in blood pressure. In one patient latent tuberculosis was reactivated. In 2 patients in the 10 mg group, antinuclear antibodies without clinically overt symptoms of autoimmune disease developed.

The extraocular manifestations of BD did not respond as well; especially folliculitis and oral aphthous ulcers in individual patients did not respond to treatment.

Finally, patients relapsed when infliximab was discontinued for more than 12 weeks. It remains to be determined if these relapses can be prevented by longterm administration and if infliximab can ever be discontinued without relapses of ocular attacks.

Thus, when comparing these results to those from our own open label study on interferon-α2a (IFN-α2a) for treatment resistant posterior or panuveitis in BD[6,7], they seem very similar with respect to the rate of response, which was 92% in our 50 patients. There were similar adverse events at comparable frequency; however, due to the different mode of action of IFN, which is more immunomodulatory than immunosuppressive, infections were not observed. In contrast, psoriasis occurred and autoimmune thyroiditis was seen in 2 and 3 patients, respectively, with IFN-α2a. With IFN-α2a we also observed differential efficacy, meaning that although ocular manifestations dramatically improved, oral aphthae did not[7]. Visual acuity improved from 0.56 to 0.84 after 24 weeks. In more than 60% of the patients (unpublished data, at the time of publication 40%) IFN has been stopped without relapse. This has not been shown for any other treatment of BD uveitis up to now. We recently published the first results for the visual acuity after 5 years, and were able to show that the improved visual acuity after IFN treatment was preserved — the 5-year data after IFN are significantly better when compared to those for immunosuppressants[8]. Thus, considering and comparing the data published until now (and we are not the only group with positive experiences with IFN-α for ocular BD — Wechsler, *et al* from Paris and Krause, *et al* from Berlin published similar results[9,10]), IFN-α appears to be at least as effective as infliximab, providing quick responses (time to response 2 weeks) and having similar, possibly less serious side effects. The main advantage of IFN-α is the possibility of discontinuation of treatment without relapse and the preservation of visual acuity.

Prof. Rosenbaum states in the corresponding editorial to the article of Ohno, *et al*[11] that he would certainly prefer TNF antagonists to IFN for the treatment of resistant ocular BD. This is his personal opinion, which he explains with his own experience, being much better for 9 patients treated with infliximab and inferior for an unnamed number of IFN treated patients. He may have used IFN in combination with immunosuppressants, which is counterintuitive, because most immunosuppressants, especially glucocorticoids, block exactly those signal transduction pathways IFN utilizes for its diverse effects on the immune system and thus diminish its efficacy. We, too, treated 2 patients who did not respond adequately to IFN with infliximab, and achieved remission of ocular inflammation. In our experience, when using it as a monotherapy, IFN-α2a is effective in over 90% of the cases, and this has not changed after publication of the data on 50 patients in 2003. As IFN can be discontinued without relapse in at least 50% of the patients and is much cheaper than infliximab in a dosage of 5 to 10 mg/kg, and the number of studies and case reports on IFN for BD, and thus the number of published patients treated, is much higher for IFN-α (more than 300, summarized in[12]) than for infliximab (about 40), in these times of evidence-based medicine, we would primarily treat our treatment-resistant patients with ocular BD with IFN, and in case of inefficacy, switch them to infliximab.

As Prof. Rosenbaum states, a randomized controlled trial is necessary, but first, each of the agents discussed here (IFN-α2a and infliximab) should be tested against the standard immunosuppressive regimen (e.g., CSA plus steroids) and then, in a second step, when proven superior to or at least adequate to the standard, against each other. We have just started a national randomized, single-blind trial of IFN-α2a versus CSA in Germany and hope that a similar trial will be done for infliximab.

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Dr. Ohno replies

To the Editor:

In response to the comments of Dr. Kötter, *et al* about our article we would like to highlight the following important points: We chose dose settings of 5 mg and 10 mg/kg body weight. The dose setting of 10 mg was derived from results of multiple administration studies of infliximab on patients in Europe and the US. Ten milligrams infliximab was the highest dose administered to rheumatoid arthritis and Crohn's disease (CD) patients in the aforementioned studies. The dose of 5 mg was based on the dose administered to CD patients without the coadministration of immunosuppressants, such as methotrexate. As for the emergence of neutralizing antibodies, we detected only one positive case within the 5 mg group. While only 7 cases were assessable due to the interference of infliximab, we cannot necessarily conclude that neutralizing antibodies will be more likely to develop when higher dosages are administered.

As a secondary endpoint we also evaluated extraocular symptoms. However, the evaluation of extraocular symptoms proved difficult due to the small number of patients who had such symptoms at screening.

Finally, as reported, we conducted a longterm retreatment study of patients with Behçet's disease (BD) and refractory uveoretinitis, who had responded to infliximab previously[1]. In this particular study, patients were given the same dose of infliximab that had previously been administered at Weeks 0, 2, and 6, then every 8 weeks. Eight patients were enrolled in this study and the results showed that the frequency of ocular attacks was greatly diminished when compared to the period preceding treatment with infliximab.

Dr. Kötter, *et al* state in their letter that interferon-α (IFN-α) used on resistant posterior uveitis or panuveitis in BD would be as effective as infliximab and would have less serious side effects. However, we feel it is necessary to devote more careful attention to the demographic differences of the patients upon whom these 2 different drugs were tested.

Although it was not clear in the report from Kötter, *et al* how severe the symptoms were in the patients who were given IFN-α^2, we would like to emphasize that in our study we enrolled patients with relatively severe disease, that is, patients who fulfilled the following set of criteria: (a) at least one ocular attack during the retrospective period; (b) at least one ocular attack during the observational period; (c) at least 3 ocular attacks during the combined retrospective and observational periods.

Also, the average visual acuity of patients at screening was 0.56 in the study of Kötter, *et al* and only 0.03 in our study, even during remission. This implies that there may be some differences in the focal points of these 2 studies.

Although there may be some further tasks to undertake, our current results indicate that infliximab is useful for BD patients with uveoretinitis whose symptoms cannot be sufficiently controlled by standard therapies, and that infliximab offers new possibilities as an effective therapeutic option for these patients.

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Do Male Patients with Primary Sjögren's Syndrome Have a Higher Frequency of Autoantibodies?

To the Editor:

The higher prevalence of autoantibodies found by Díaz-López, *et al*[1] in their male patients with primary Sjögren's syndrome (SS), compared with that found in a large series of female patients with a similar mean age, is somewhat surprising and contrasts with previous reports. We would like to analyze various methodological aspects of their article.

First, the main conclusion of the study is in opposition to a generally accepted idea in autoimmunity, namely, that a higher degree of autoimmune activity (both clinical and serological) is found in women compared with men. Various reports demonstrated this higher rate of autoimmune abnormality in females, including a higher frequency of autoantibodies among healthy females[2], higher levels of serum immunoglobulins[3], and stronger humoral and cell-mediated immune responses[4] in women. These differences are especially marked in patients with autoimmune diseases characterized by B cell hyperreactivity, such as systemic lupus erythematosus or primary SS.

Second, the authors have not included previous reports that specifically analyzed gender differences in large series of patients with primary SS[5-8], all of which found results in opposition to the present study. We have recently analyzed a large series of patients with primary SS using the same classification criteria and including patients from the same geographical area, and found a significantly lower prevalence of antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-Ro/SSA antibodies in 27 male patients compared with 363 females with primary SS[6]. Other recent studies have found a lower prevalence of clinical, histopathologic, and sialographic abnormalities in male SS patients[7,8]. All previous studies[5-12] have described a lower autoimmune expression (whether clinical, histological, sialographic, or immunological) in male patients with primary SS, in contrast to the study by Diaz-Lopez, *et al*[1].

Third, the atypical epidemiologic and clinical characteristics of the 549

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patients presented by Diaz-Lopez, *et al*[1] deserve specific consideration. The mean age of female patients in the Diaz-Lopez series (64 years) is notably higher than that reported in the recently published large series[6,13,14], in which the mean age was at least 10 years lower. In addition, it is surprising that the authors state that "all our females are post-menopausal." Were none of their 521 female patients pre or peri-menopausal?

The clinical characteristics of the patients are also unusual. In the description of the systemic involvement of patients, the authors include several nonspecific, nonautoimmune manifestations highly prevalent in the general population, which are not usually considered as part of the extraglandular involvement typical of primary SS, such as carpal tunnel syndrome, osteoarthritis, or fibromyalgia. In contrast, the prevalence of the main typical and specific extraglandular features of primary SS (cutaneous vasculitis, neurological, pulmonary, renal, muscular...) is not detailed. Although systemic SS involvement seems to be included under the term "other clinical visceropathy," the frequency stated (only 5% of patients) is unexpectedly low, and contrasts greatly with that found in other large series[6,15], in which these extraglandular features are usually observed in 20–30% of patients.

Fourth, the immunological profile of the 521 females presented by Diaz-Lopez, *et al*[1] should also be carefully analyzed. The extremely low prevalence of autoantibodies in their female SS patients (60% ANA, 28% RF, 18% anti-Ro, and 9% anti-La) is not reflected in previous studies (Table 1). It is difficult to explain these extremely low prevalences, other than possible methodological differences. These low prevalences in women mean that the comparison with men assumes statistical significance. Specifically, it is striking that less than 20% of 521 female SS patients are Ro/La positive, since previous studies report a prevalence for anti-Ro/SSA ranging between 41% and 63% (only 18% in the study), and for anti-La/SSB between 20% and 27% (9% in the study).

Table 1. Prevalence of autoantibodies in female patients with primary SS.

	Females, n	ANA, %	RF, %	Ro/SSA, %	La/SSB, %
Molina[9]	69	55	51	45	20
Anaya[10]	25	79	60	62	35
Drosos[11]	30	77	53	63	37
Brennan[12]	28	86	54	61	36
Garcia-Carrasco[6]	363	74	42	41	27
Diaz-López[1]	521	60	28	18	9

In summary, it seems that the profile of the female patients reported by Diaz-Lopez, *et al* is atypical, both epidemiologically (higher mean age), clinically (high presence of noninflammatory disorders and extremely lower presence of classical extraglandular SS features), and immunologically (only 18% of females being Ro/La positive). This profile is very different from that usually described in patients with primary SS. The higher prevalence of autoantibodies in male SS patients found by Diaz-Lopez, *et al*[1] is in contrast to our clinical experience and that of other groups working in the field of primary SS.

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Dr. Díaz-López, *et al* reply

To the Editor:

We thank Dr. Ramos-Casals and co-workers for their comments on our article[1]. We agree that our data are contradictory to some previous reports and would like to raise some points in answer. Concerning the first 2 comments on methodological aspects, there is a general consensus that autoimmune processes are present in women more often than in men, and that Sjögren's syndrome (SS) in men is infrequent. Higher levels of autoantibodies and B cell hyperreactivity are frequently seen in patients with systemic lupus erythematosus (SLE) and SS. Therefore, we agree with the authors on that point, as we also do about the absence in our bibliographic citations of articles on large series of patients with SS analyzing gender differences[2].

In answer to the second and third suggestions, as we pointed out in our article, our findings contrast with other reports[3-5] because of the higher prevalence of elevated rheumatoid factor (RF) and antinuclear antibodies (ANA) in men than in women, but we explained our final data based on a number of factors: (1) the mean age of patients included, (2) the small sample of men with primary SS, and (3) the biphasic dose effect of estrogens and other hormones. Our data come from more than 550 Rheumatology

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Unit outpatients with primary SS between 1993 and 2001, and only 28 consecutive male patients were diagnosed and followed during this period. Although we also have young patients, the majority of our patients are older, which might explain a higher incidence of immunological problems being more evident in male patients. However, we suggest that prospective multicenter clinical and serological trials be undertaken in a larger group of men with primary SS.

We agree with Ramos-Casals, *et al* that we have labeled all our patients postmenopausal, and we have to recognize that this is not entirely correct. Approximately two-thirds of our patients were peri- and post-menopausal, but not all. Thus, this higher mean age could explain the clinical characteristics of our sample of patients and the difference with some recent published series.

We included the pattern of several nonspecific manifestations, such as carpal tunnel syndrome, fibromyalgia, and erosive osteoarthritis, which are increasingly present in patients with primary SS and are common complaints in daily rheumatology practice, whereas the extraglandular manifestations, such as vasculitis, lung, kidney, and muscular disorders, are present in a low percentage (5–10%). Our explanation is that, while our rheumatolgy unit receives a large number of patients with low to moderate disease, Ramos-Casal *et al*'s Internal Medicine Department might receive more severe patients with more extraglandular diseases.

Concerning the extremely low prevalence of autoantibodies present in our final results as mentioned by Ramos-Casals, *et al*, we should point that all our patients fulfilled 4 or more diagnostic criteria for SS, as proposed by the European Community Study Group in 1993, and diagnostic tests were applied according to the recommendations of the European Community Study Group[6]. All had at least one of the immunological criteria (RF, ANA, Ro, La, gland biopsy), meaning that none of our patients was seronegative. These criteria compared with those of Fox, *et al*[7] are very sensitive, but their specificity is low, so that the diagnosis of primary SS is much easier to accomplish. Using more restrictive criteria, such as the Fox criteria, probably might explain the higher frequency of extraglandular manifestations and Ro antibodies (80%). We diagnosed our primary SS patients with SSA/Ro and SSB/La by using 4 techniques: immunodiffusion, immunoblotting, ELISA 52 and 60, and RNA immunoprecipitation; we did not detect differences between them, supporting the hypothesis that correlates more severe disease with greater prevalence of antibodies. Therefore, we think that Ramos-Casals's group has a sample of patients with more severe disease.

In summary, we consider that our results cannot be considered atypical: we describe cases of primary SS patients with less severe disease and more rheumatic complaints attending the general rheumatology clinic, instead of more severe patients with more extraglandular manifestations. On the other hand, we suggest that further studies using the new USA-EU criteria would be of interest to reach a consensus on primary Sjögren's syndrome[8].

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Book review

Physical Rehabilitation in Arthritis. J. Walker, A. Helewa, Editors. St Louis: Saunders, 2004, 414 pages, price $69.95 (US).

I congratulate the authors for this significantly updated second edition. They lead the way in standardized interdisciplinary approaches to chronic disease management in the field of rheumatology. Although there is some redundancy between chapters, this textbook is thoughtfully written with useful, at-a-glance tools, such as algorithms at the beginning of each chapter and recurring boxes presenting key facts or competencies. It adds clarity to understanding a group of highly complex diseases and presents multidimentional intervention strategies. Students and clinicians alike will find well presented concepts followed by their practical applications. It also provides a considerable amount of published data by systematically presenting current clinical practice guidelines, metaanalyses, and results of relevant research studies. However, the chapter on fibromyalgia does present some weakness in terms of the quality and quantity of the evidence provided. In general the book promotes knowledge transfer and challenges our way of thinking about treating patients in rheumatology. In my opinion no student of the rehabilitation sciences or healthcare professional working in the field of rheumatology should be without this reference text.

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