

## LETTERS

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### Disseminated *Salmonella typhimurium* infection secondary to infliximab treatment

To the Editor:

We read with interest the review by Ellerin et al on infections and anti-tumor necrosis factor (anti-TNF) therapy (1), as well as the article by Netea et al reporting 2 cases of *Salmonella enterica* septicemia secondary to treatment with adalimumab and infliximab (2). Netea and colleagues also demonstrated decreased interferon- $\gamma$  production and inhibition of Toll-like receptor 4 expression on dendritic cells in anti-TNF-treated rheumatoid arthritis patients, providing a potential explanation for the increased susceptibility to intracellular organism infection associated with anti-TNF therapy.

We have recently seen a patient with disseminated *Salmonella typhimurium* infection secondary to anti-TNF therapy. This is, to our knowledge, the first published report of such a finding. The patient was a Fijian Indian man who developed psoriasis and psoriatic arthritis in 1992. He migrated to Australia in 1993. His skin and joint disease remained very active despite a variety of treatments administered over a period of years, including psoralen ultraviolet A, acitretin, sulfasalazine, methotrexate, and cyclosporine. At the time of presentation to us in January 2003, at the age of 39 years, he was taking prednisone (10 mg/day) and sulfasalazine. His erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were both elevated (ESR 80 mm/hour [normal  $\leq 10$ ], CRP 82 mg/liter [normal  $< 3$ ]). Cyclosporine treatment was reinstated in late January 2003 and was mildly efficacious, but was discontinued in early April due to intolerable side effects including hypertension, headaches, and impairment of short-term memory. In mid-April 2003, treatment with infliximab combined with methotrexate (7.5 mg/week) was started. Infliximab infusions (5 mg/kg) were given at weeks 0, 2, 6, 14 and 22, with dramatic clinical response. At week 2, the swollen and tender joint counts were 0 and the ESR and CRP were 7 mm/hour and  $< 1$  mg/liter, respectively. The patient's psoriasis also improved rapidly, and the Psoriasis Area and Severity Index score was 0 at the time of the third infusion. Prednisone and sulfasalazine were discontinued after the third infusion.

During the twenty-eighth week of infliximab therapy, the patient presented with a 2-day history of fever, chills, rigor, headache, and myalgia. His temperature was 41°C. No other specific abnormalities were detected on physical examination. He was admitted to the hospital. Laboratory investigations revealed a CRP level of 226 mg/liter and an ESR of 53 mm/hour. *S typhimurium* was isolated from 5 of 6 blood cultures. The patient was treated initially with intravenous (IV) ceftriaxone, and then with IV ciprofloxacin after identification of the organism. The fever resolved after 4 days of IV antibiotic treatment, and he was discharged from the hospital after 10 days, with no complications.

*S typhimurium* is the second most frequently isolated *Salmonella* serotype from human sources, after *Salmonella*

*enteritidis* (3). Infection often results in self-limited gastroenteritis, and the diarrhea typically lasts 3–7 days. Only 1–4% of immunocompetent individuals have positive blood cultures (4). The risk of disseminated salmonellosis is increased in immunocompromised patients.

This case demonstrates that patients receiving anti-TNF therapy may present with manifestations secondary to disseminated infection rather than with localized symptoms as might be expected in immunocompetent patients, and parallels the unusual patterns of presentation of *Mycobacterium tuberculosis* infection in the setting of anti-TNF $\alpha$  therapy (5). Hess et al (6) demonstrated decreased adherence of *S typhimurium* to cultured intestinal epithelial cell lines after the lines were pretreated with TNF $\alpha$ . This could be one possible explanation for the increased risk of disseminated salmonellosis in patients treated with TNF $\alpha$ -blocking agents.

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### Results of anakinra treatment in rheumatoid arthritis patients previously treated with tumor necrosis factor $\alpha$ blockade: comment on the article by Buch et al

To the Editor:

We read with interest the report by Buch and coworkers showing that patients with rheumatoid arthritis (RA) that fails to respond to tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) blockade also do not show response to interleukin-1 (IL-1) receptor antagonist

treatment (1). At the national meeting of the Swedish Rheumatological Society in 2003, we presented results from our observational study of biologic agents in southern Sweden, which support and extend the findings reported by Buch and coworkers. As of August 2003, the South Swedish Arthritis Treatment Group had records on 1,272 treated RA patients (1,591 treatment courses) (2). Among these, we identified all patients treated for at least 3 months with anakinra ( $n = 26$ ) and subdivided them into those not previously treated with biologic agents ( $n = 10$ ), those previously treated with TNF $\alpha$  blockade who responded according to the American College of Rheumatology 20% improvement criteria (ACR20) (3) but had stopped the treatment due to side effects ( $n = 7$ ), and those previously treated with TNF $\alpha$  blockade who did not fulfill the ACR20 ( $n = 9$ ). The patients in the 3 groups were similar with regard to age (median 59.1 years), disease duration (median 12.6 years), ongoing prednisolone treatment, and number of previous disease-modifying antirheumatic drugs (median 4.5). The mean 28-joint-count Disease Activity Score (4) at the time of initiation of anakinra treatment was 6.1, and the median interval between the discontinuation of previous biologic treatment and the start of anakinra treatment was 252 days. Patients were treated with 100 mg of anakinra subcutaneously daily.

ACR20 response at 3 months was reached in 30% (3 of 10) of the patients not previously treated with a biologic agent, 57% (4 of 7) of those who discontinued TNF $\alpha$  blockade treatment due to side effects, and 22% (2 of 4) of those who discontinued TNF $\alpha$  blockade treatment due to inefficacy. ACR50 response (5) at 3 months was reached in 10%, 29%, and 0% of the patients in these groups, respectively. Moderate response according to the European League Against Rheumatism (EULAR) criteria (6) was achieved in 60%, 43%, and 33%, and good response according to the EULAR criteria in 10%, 14%, and 11%, respectively (i.e., 1 patient in each group).

This small study shows that patients whose RA fails to respond to TNF $\alpha$  blockade rarely show any clinically meaningful response to anakinra. The results in patients not previously treated with biologic agents are also disappointing. It is somewhat surprising to note that the best outcome according to ACR response criteria at 3 months was observed in the patients whose RA had responded to TNF $\alpha$  blockade but who had to stop this treatment due to side effects. This finding should be interpreted with caution since the number of patients is small, but it is tempting to suggest that both types of biologic agents affect common pathways in the disease process, in accordance with the hypothesis that there is a hierarchy, with TNF $\alpha$  being the dominant cytokine (7). According to this hypothesis, blocking of TNF $\alpha$  would be the most effective treatment, but blocking of IL-1 may be efficacious to a certain extent. More work is needed to elucidate this. We would argue that before firm conclusions on the role of IL-1 blockade for the treatment of RA are drawn, an agent with more efficient IL-1-blocking properties than anakinra needs to be developed.

In conclusion, we agree with Buch and coworkers that anakinra is not effective for the treatment of RA patients who have been treated unsuccessfully with TNF $\alpha$  blockade. However, the possibility that IL-1 blockers with more favorable

pharmacokinetic/dynamic properties may be efficacious cannot be ruled out.

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## Reply

To the Editor:

My colleagues and I thank Dr. Saxne et al for their remarks and note that their RA patients who discontinued TNF blockade treatment due to inefficacy ( $n = 7$ ) had a disappointing response to treatment with the IL-1 receptor antagonist comparable with findings in our anakinra study: 22% of such patients in their study achieved an ACR20 response and 33% a EULAR moderate response, compared with 8% and 33%, respectively, of the 26 patients in our study in whom TNF $\alpha$  treatment had been inefficacious (and none of their patients in this subgroup had an ACR50 response). Saxne and colleagues also include results from patients who had not previously been treated with biologic agents ( $n = 10$ ), in whom an ACR20 response rate of 30% and a EULAR moderate response rate of 60% were observed. We have instituted anakinra treatment in 30 patients not previously treated with

biologic agents, and although the ACR20 response rate was only 17% (0% ACR50), 50% achieved a EULAR moderate response (0% good).

The fact that there is a very poor response to anakinra after failure of TNF antagonist treatment (and perhaps a slightly better response in patients who have not received other biologic treatment) (Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;50:607–12) is consistent with the suggestion by both our group and Saxne's that the IL-1-mediated pathway blocked by anakinra is similar to that of TNF $\alpha$  and consequently IL-1 antagonism in patients in whom TNF $\alpha$  blockade treatment was unsuccessful is not an effective strategy. The alternative explanation, that the low rate of response to anakinra is due to incomplete IL-1 blockade, is difficult to assess, but the impressive results seen with IL-1 blockade (anakinra) treatment of the periodic fever syndromes suggests that this agent is capable of effectively blocking the IL-1 pathway, at least in the latter disease group.

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### **Failure to report previously used drugs and dosages in pharmaceutical company-sponsored rheumatoid arthritis trials: comment on the article by Yocum et al**

*To the Editor:*

We read with interest the report by Yocum and colleagues of the efficacy and safety of tacrolimus for the management of rheumatoid arthritis (RA) (1). Prior to randomization, the investigators determined whether patients could not tolerate or had disease that was resistant to disease-modifying antirheumatic drugs (DMARDs). Although they state that lack of efficacy was rigorously predefined, no mention was made of which DMARD was used or what dosage would define failure/intolerance.

The omitted information is important, because we have noticed investigators deeming patients "DMARD failure" before the standard maximal recommended dosages of the DMARD have been instituted. Using methotrexate (MTX) as an example, the reader could easily assume that patients in the study by Yocum et al were considered MTX intolerant (if MTX was used) at a dosage of approximately 10–15 mg/week, because several other investigators have done this (2–6), even though the American College of Rheumatology (ACR) considers the maximal standard maintenance dosage to be as high as 20 mg/week (7). We admit that keeping MTX dosages below the maximal standard maintenance dos-

ages set forth by the ACR should make a competitor drug relatively more effective. Regarding the DMARD used, readers may anticipate that the response to a biologic DMARD may be different from that to medications such as hydroxychloroquine or sulfasalazine.

Failure to report the meaningful information regarding individual DMARDs used or the DMARD dosages administered before patients are considered "DMARD intolerant" or "DMARD failures" diminishes the clinical utility of the study for the reader.

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### **Reply**

*To the Editor:*

We appreciate the opportunity to discuss the comments by Drs. Parker and Rennie regarding the criteria used to determine DMARD resistance and DMARD intolerance and to discuss the conclusions of our article.

Our study was performed in order to develop an additional therapeutic option for patients in whom treatment with 1 or more DMARDs had failed. DMARD resistance and DMARD intolerance were defined in the protocol as resistance or intolerance to the most recent DMARD received for

**Table 1.** Guidelines for defining minimum dosage and duration for DMARD resistance\*

DMARD	Dosage	Duration
Methotrexate	15 mg/week	2 months
Azathioprine	1.5 mg/kg/day	3 months
Sulfasalazine	2 gm/day	3 months
Cyclophosphamide	1.5 mg/kg/day	3 months
Cyclosporine	2 mg/kg/day	2 months
Leflunomide	20 mg/day	2 months
Etanercept	25 mg subcutaneously twice weekly	1 month
Auranofin	6 mg/day	6 months
Injectable gold	50 mg/week, 800 mg total	16 weeks
Penicillamine	500 mg/day	3 months
Hydroxychloroquine	400 mg/day	3 months

\* DMARD = disease-modifying antirheumatic drug.

treatment of RA. This definition applied to any DMARD therapy and was used to ensure that no patient whose RA was responding to his or her current therapy would be taken off that therapy in order to participate in the study of tacrolimus, a drug whose efficacy in RA had not yet been entirely proven at the time the protocol was initiated. DMARD resistance was defined as “continued active RA despite receiving a therapeutic dosage of a specific DMARD for a duration of time typically sufficient to elicit a therapeutic response.” Guidelines defining the minimum dosage and duration of treatment necessary to define DMARD resistance for the DMARDs that were approved in the US at the time the protocol was written were included in the protocol and are shown in Table 1. DMARD intolerance was defined as “the inability or unwillingness . . . to continue therapy due to an adverse drug experience.”

It is important to clarify what appear to be misinterpretations by Drs. Parker and Rennie. First, the rigorously predefined lack of efficacy to which they refer in their letter was applicable to the reason for withdrawal from the study and not to previously used DMARDs. Second, they suggest that previously used DMARDs were kept at a below-standard maintenance dosage. As indicated in Table 1, standard maintenance dosages for all DMARDs were included in the guidelines. In addition, it is important to note that in our trial we did not study add-on therapy, a situation in which their comment might apply. Rather, we studied the efficacy of tacrolimus in patients in whom other DMARDs had failed. Of note, one of the conclusions from our study was that patients who were resistant to a previous DMARD were less likely to have a robust response to tacrolimus. Third, the purpose of our study was not to rigorously define when a patient has failed DMARD therapy and when an additional or alternative DMARD should be instituted. That discussion is one that must occur between the patient and his or her physician. The study described in our article was done to increase therapeutic options available to both patient and physician and thereby allow more patients with RA to achieve a therapeutic response.

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### **Radiographic progression in early rheumatoid arthritis: comment on the article by Goronzy et al**

*To the Editor:*

We read with interest the article by Goronzy et al on prognostic markers of radiographic progression in early rheumatoid arthritis (RA) (1). The authors analyzed baseline prognostic markers, including multiple genetic factors, for progression of hand erosions in a series of patients with early RA, after 2 years of followup. They used a standardized treatment protocol algorithm starting with hydroxychloroquine, in order to avoid aggressive overtreatment. They claim that in other studies of the progression of radiographic damage in early RA, a predefined treatment strategy was not used. We recently conducted a study of RA radiographic progression in a clinical setting after 1 year of followup (2). All patients were also enrolled in a structured treatment protocol using disease-modifying antirheumatic drugs (gold salts and/or methotrexate) and low-dose glucocorticoids, and response (according to the American College of Rheumatology [ACR] definition [3,4]) was taken into account. As in the study by Goronzy and colleagues, some factors, such as radiographic damage at baseline and shared epitope homozygosity, were found to be associated with progression.

We are very impressed by the good therapeutic response among patients in the study by Goronzy et al. After 6 months, 78 of 105 patients (74%) met the ACR 50% improvement criteria (in our study this percentage was 53.3%). In addition, methotrexate treatment was needed by only 43% of their patients during the 2 years of followup. How can the excellent rates of treatment response in that study, in compar-

ison with ours and other studies using hydroxychloroquine, a drug considered to have a modest therapeutic effect in RA (5), be explained? Although the short disease duration of Goronzy and colleagues' patients at study enrollment (mean 6 months), the high percentage of patients who were negative for rheumatoid factor (41.8%), and the type of population analyzed (recruited from the local community) may partly explain these high response rates, we believe other, as-yet-unknown, factors may also contribute to the strikingly benign disease evolution. Moreover, recent studies do not support the notion that RA in the community population has a benign course (6). Thus, it would be interesting to know the number of patients in whom complete remission was achieved and the percentage and clinical course of patients with seronegative disease or with disease duration of <3 months at enrollment. It has been reported that, in these patients, the rate of remission was very high and probably unrelated to antirheumatic therapy (7). Moreover, the measurement of specific serologic markers of RA, such as anti-cyclic citrullinated peptide antibodies (8), would be of interest in order to better classify this type of arthritis in the early stages.

In conclusion, the study by Goronzy et al makes important contributions to the knowledge of factors related to radiographic progression in early RA, but in our opinion, the unexpected benign course in the patients reported is difficult to explain, and extrapolation of the results to other populations with early RA is questionable.

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## Reply

*To the Editor:*

Sanmarti et al raise the question as to whether patients with RA enrolled in our prospective study had unusually benign disease compared with other prospective cohorts, in particular, the one they have followed up in Spain at the Hospital Clinic of Barcelona and Hospital Parc Tauli of Sabadell (Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Suris X, et al. Radiological progression in early rheumatoid arthritis after DMARDS: a one-year follow-up study in a clinical setting. *Rheumatology [Oxford]* 2003;42: 1044–9). There have been few prospective studies that have explored prognostic markers and used predetermined treatment algorithms, among them the cohort study reported by Sanmarti and colleagues in 2003 (we did not claim that our study was the only one, as they imply). If one compares these studies carefully, the outcome results are actually quite similar and within the margin of error given the sample sizes: the Spanish cohort had 60 patients and our cohort had 111 patients. Specifically, after 1 year (a comparison of the data after 2 years is not possible because the followup in the Spanish study was only 1 year), 38% of the Spanish patients had not achieved an ACR50 response and were taking methotrexate. The ACR50 response rate in the US cohort was almost identical at 57%. Seventy-four percent of the Spanish patients had no progression in the number of erosions within 1 year, again very similar to the US patients, who on average gained 1 erosion per 2 years and of whom 48% did not have any erosive progression over 2 years.

It is correct that the 2 studies had slightly different demographics; the Spanish study allowed for the enrollment of patients with disease duration up to 2 years and showed that longer disease duration was associated with more radiographic progression, whereas the US study only enrolled patients who had had symptoms for <1 year. However, there is no indication that patients enrolled in our study did not have RA but rather had a self-limited arthritic disease. Complete remission after 2 years and change in diagnosis were the rare exceptions, even among patients whose disease duration was <3 months at the time of enrollment. Also, ~10% of our patients who were negative for rheumatoid factor at enrollment subsequently became positive, and the percentage of rheumatoid factor-positive patients was comparable in the 2 studies.

Thus, the lesson from both studies is that there is a subset of patients with RA who tend to do well with nonaggressive treatment. Prognostic markers are needed to identify

such patients in order to avoid overtreatment, particularly if we move from a step-up treatment strategy to an early aggressive approach.

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**Ultrasonography of the shoulder in patients with rheumatoid arthritis: comment on the article by Hermann et al**

*To the Editor:*

We read with interest the article by Hermann et al (1), reporting on a study in which they compared 3 imaging methods in rheumatoid arthritis (RA) patients with shoulder pain. They detected erosions of the glenohumeral joint by radiography in 60% of patients, by ultrasonography (US) in 70%, and by magnetic resonance imaging (MRI) in 91%. Although US was superior to conventional radiography in detecting erosions, significantly more erosions of the humeral head were detected by MRI than by the other 2 imaging methods. MRI was also superior to US in identifying synovitis of the glenohumeral joint (28% versus 63%), tenosynovitis of the biceps tendon (35% versus 65%); and bursitis (30% versus 42%). We would like to raise some concerns about these results.

First, the finding of the low rate of erosions by US in the RA group is difficult to understand. The quality of an US examination depends not only on the experience of the examiner, but also on the equipment. Even in healthy adults, high-resolution US detects erosions (defined as a pit in the bone surface of >1 mm diameter in all 3 diameters) in 23% of shoulders (2). The low resolution of the rather old US equipment used by Hermann and colleagues could explain the low frequency of erosions detected in the RA group. Furthermore, comparison of the rates of erosions identified by MRI and US is a perilous undertaking, since there is no international consensus regarding the definition of erosions of the shoulder as detected by US. Because there is no gold standard, it remains uncertain whether the authors' classification of erosions for US and MRI pertains to the same pathology. For example, the observed cortical defects with hypointense signal on T1-weighted spin-echo images could represent osteoarthritic changes rather than RA-related pathology.

Second, gray-scale US is an excellent method for detecting (para)articular abnormalities such as synovial membrane thickening and proliferation, joint effusion, bursal effusion, peritendinous effusion, and rotator cuff tears (3). The authors stated that their US findings of glenohumeral joint effusion (28%), biceps sheath effusion (35%), and fluid within the bursa (30%) were consistent with those in a study by Alasaarela et al (4), but in fact they were not. The latter group

reported these abnormalities in 92%, 83%, and 89%, respectively, of cases. This large discrepancy between the results of Hermann et al and those of Alasaarela et al again raises concerns about the quality of the US equipment. It is also a pity that the authors did not compare clinical examination for soft tissue changes with US and MRI findings. Although US may be less sensitive than MRI, it is likely to be more sensitive and specific than clinical examination.

Third, Hermann et al limited their examination to the glenohumeral joint. As control subjects, they examined individuals with shoulder pain. However, it is well known that shoulder pain may originate from the acromioclavicular joint, which appears to be involved more often than the humeroscapular joint in patients with RA (5). This raises questions as to whether the authors examined the correct joint. Examining both the glenohumeral and the acromioclavicular joint could have settled this issue.

We would like to make a final point. The report by Hermann and colleagues focuses on erosions in the shoulder joint. However, considering the fact that erosions in the glenoid fossa cannot be visualized by US it is questionable whether US should be used in the first place for this purpose. We believe the future of US lies in the direction of visualization of synovitis and bursitis, and making the distinction between inflammatory and noninflammatory disease.

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**Reply***To the Editor:*

We appreciate the detailed observations by Bruyn et al concerning our study comparing conventional radiography, US, and MRI of the shoulder joint in RA. Their critical comments highlight the fact that investigators are far from agreement on the most suitable imaging modalities for the diagnostic assessment of RA, and provide a good starting point for fruitful discussion.

Bruyn and colleagues raise 3 major issues. First, they express doubt about the low rate of detection of erosions by US, which they partly attribute to the low resolution of the US equipment used in our study. We did indeed use a US machine with average performance and a maximum frequency of 7.5 MHz. However, we deliberately chose this machine because it is the standard equipment typically used by rheumatologists. State-of-the-art US equipment with high-resolution linear transducers (>10 MHz) is available at our institution for future studies but is currently not in wide use in the routine diagnostic setting. The rate of detection of erosions in our study was 70% with US and 91% with MRI. These are below the rates reported by Alasaarela et al (1,2). All assessable areas of the humeral head were very carefully evaluated ultrasonographically in our study, by a rheumatologist experienced in the field of musculoskeletal US. Superficial bone lesions are clearly identified by US, while deeper erosions are not accessible and are better identified by MRI. Another reason for the difference in the detection of erosions by US and MRI between Alasaarela and colleagues' study and ours is the fact that we used high-resolution 1.5T MRI and a high-resolution matrix of up to 512 pixels, while they performed MRI at 1.0T. The thin slice thickness of 3 mm used with some sequences likewise improves the detection of very small erosions by MRI.

Bruyn et al quote the most recent study on the US morphology of clinically healthy joints (3), which was performed with state-of-the-art US equipment and yields interesting new insights. That study identified changes of the shoulder joint resembling RA erosions in up to 23% of cases. The 10 patients in our control group were examined only by MRI and did not undergo US. MRI depicted erosive lesions in 20% of the controls, which is comparable with the above-quoted results found by Schmidt et al (3). However, this finding needs to be verified in larger study groups. It would be useful to know whether Schmidt et al confirmed the bone lesions they identified in healthy subjects with other imaging modalities (conventional radiography, MRI). It is well known that shoulder lesions become symptomatic later because the shoulder joints are exposed to less strain than the legs. Moreover, the term "erosions" should not be used to refer to changes of the head of humerus in healthy subjects. The term "bone lesions" is more appropriate, and these are most likely due to degenerative changes. Furthermore, it is important to confirm these changes using other imaging modalities, in particular, to determine whether the changes are cystic bone lesions.

Second, Bruyn et al comment on our results concerning the detection of soft tissue lesions such as synovitis, tenosynovitis, and bursitis by US and compare these with the findings published by Alasaarela et al (1). Synovitis was demonstrated by US in 28% of our study patients, as opposed

to 81% of the Finnish patients studied by Alasaarela and colleagues (1). Agreement with MRI results is poor, as reflected by a kappa value of 0.29 in both studies. However, kappa values in different studies cannot be compared when the marginal distribution is not the same (4). The difference in the percentage of patients with US-detected synovitis in the 2 study populations may be attributable to several factors, such as differences in the duration of disease, rheumatoid factor status, or general disease activity. Moreover, the group of 30 patients studied by Alasaarela et al was heterogeneous: most had RA, but some had other rheumatic diseases. Alasaarela and colleagues likewise used a 7.5-MHz transducer and found the agreement between MRI and US in the detection of bursitis and tenosynovitis to be good ( $\kappa > 0.40$ ), whereas it was poor in our study population ( $\kappa < 0.40$ ).

Bruyn et al calculate a high incidence of soft tissue involvement in RA of the shoulder joint in the study by Alasaarela et al (1) by relating the number of joints positive by US to the number positive by MRI, but not to the total number of patients. This calculation is incorrect since it does not take into account the fact that MRI is not the gold standard, nor was it treated as a gold standard in our study or the study by Alasaarela and colleagues. For this reason, the possibility of false-positive findings cannot be excluded. The international OMERACT (Outcome Measures in Rheumatology Clinical Trials) group is currently discussing the recognition of MRI as the gold standard for imaging of RA changes in the small joints of the hands (5,6), but this is not presently planned for the shoulder joint.

A third issue raised by Bruyn et al concerns the acromioclavicular joint, which they suggest should have been included in our analysis. Our protocol included examination of the acromioclavicular joint, but the analysis was not included in our recent report. An additional statistical analysis of acromioclavicular joint involvement in RA would have been beyond the scope of that article, which was already quite detailed and long. This question will be addressed in a followup report.

In conclusion, we believe erosions of the shoulder joint can be identified by US as well as MRI. The latter appears to be superior in that it depicts all portions of the joint including the glenoid fossa. US has an important role in assessing soft tissue involvement in RA since it is widely available and clearly differentiates inflammatory and noninflammatory changes, and also has a higher sensitivity and specificity compared with clinical examination (7). MRI has a role as a problem-solving tool. Definitive conclusions regarding the discrepancies in the incidence of individual US findings in comparison with MRI findings among various studies can be drawn only on the basis of multicenter studies conducted using different equipment and involving different examiners.

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**Electroretinograms of children born to mothers treated with hydroxychloroquine during pregnancy and breast-feeding: comment on the article by Costedoat-Chalumeau et al**

*To the Editor:*

We read with interest the article by Costedoat-Chalumeau et al (1), who reported evidence that hydroxychloroquine (HCQ) therapy during pregnancy is safe for the fetus. In particular, no vision, hearing, growth, or developmental abnormalities were found in any of the 119 children at the last followup (mean age 26 months). We would like to add information on our experience in performing flash electroretinography (ERG) in a small group of babies who had been exposed to HCQ in utero.

In our pediatric department we routinely follow up children born to mothers with autoimmune diseases, irrespective of maternal treatment and autoantibody status. We usually perform ophthalmologic examination with funduscopy in babies whose mothers had taken HCQ during pregnancy. In 2003 we also performed ERG in 6 of these babies, all of whom had been exposed to HCQ in utero and were being seen by us for the first time. For infants and young children, in whom visual field examination cannot be performed, ERG is an additional tool with which to seek evidence of possible adverse vision effects. The characteristics of the study children are shown in Table 1. All babies were born without malformations or major complications, and at the time of examination they were all in good general health, with growth and development appropriate for age. ERG was performed successfully in all cases, and all results were normal.

ERG measures the retinal response to a stimulus of light, using surface electrodes placed on the lower lid. It provides objective information on global retinal function and enables the examiner to distinguish between different retinal disorders. In the 6 babies we studied, binocular repeated stimulation with a standard flash white light from a distance of 15 cm was performed during spontaneous sleep, without pharmacologic mydriasis. Electrodes recorded the retinal potentials that developed as a response. Two repeated measures after at least 15 flashes were analyzed and averaged. Both oscillatory potentials and combined maximal response were simultaneously analyzed. As noted above, results were normal in all cases.

Although HCQ treatment is thought to be safe during pregnancy (2-4), there has been no definite consensus on this (5). The recent demonstration that HCQ crosses the placenta (6), with cord blood concentrations nearly identical to those found in maternal blood, emphasizes the need for careful evaluation of the fetuses and newborn babies of women who received HCQ during pregnancy. Among the potential adverse effects of HCQ, retinal toxicity is of concern, and abnormalities on ERG have been associated with HCQ treatment (7). In the study by Costedoat-Chalumeau and coworkers (1), data on the children were collected from mothers, general practitioners, and/or pediatricians, but ophthalmologic examinations

**Table 1.** Characteristics of the study infants and exposure to HCQ in utero\*

Patient	Age, months/ sex†	Gestational age, weeks	Neonatal weight, gm	Apgar score, at 1 minute/ 5 minutes	Maternal diagnosis	Age of mother at delivery, years	HCQ exposure in mother‡	
							Continuous duration	Total cumulative dose, gm
1	9/F	38	2,250	7/8	SLE	32	9 years, 9 months	746
2	4/M	39	3,300	9/10	SLE	26	17 months	153
3	13/F	39	2,680	9/10	DLE	25	6 months (discontinued after 4 weeks of gestation)	69
4	30/M	41	2,480	8/9	UCTD	30	5 years, 9 months	422
5	9/M	40	2,920	9/9	SLE	26	22 months	212
6	3/M	35	2,100	8/10	SLE	41	29 months (discontinued after 19 weeks of gestation)	728

\* HCQ = hydroxychloroquine; SLE = systemic lupus erythematosus; DLE = discoid LE; UCTD = undifferentiated connective tissue disease.

† Age at which electroretinography was performed.

‡ Exposure before delivery.



were not systematically performed. However, no clinical vision abnormality was observed. Our findings provide further evidence of the retinal safety of HCQ, in accordance with previous reports (7–9). To our knowledge the use of ERG testing of children exposed in utero to HCQ has not been previously reported. All of the mothers in our study took HCQ during their pregnancies, and 5 of them took it also during breast-feeding. It is known that HCQ is excreted in breast milk, even in small amounts (10). It is noteworthy that one mother breast-fed her son for 30 months while taking HCQ (200 mg daily); ERG was performed after this long period, and even in this case the results were completely normal. Although our study sample was small, our data reinforce the observation that HCQ treatment is safe during pregnancy and lactation, even if breast-feeding is continued for many months.

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## Reply

To the Editor:

We thank Dr Cimaz and colleagues for their interest in our report. Both retinal toxicity and ototoxicity in children born to women treated with chloroquine have been reported rarely (1,2). To our knowledge, no abnormalities have been noted in relation to HCQ treatment, and we found no clinical visual abnormalities in 119 children at the last followup (mean age 26 months), as noted by Cimaz et al. Our clinical data are in accordance with those of Klinger et al, who found that results of ophthalmologic examinations and tests were normal in 14 children exposed to HCQ in utero and studied at a mean age of 1.9 years (3). In that study, ophthalmologic examinations and tests included slitlamp biomicroscopy of the anterior segment, dilated retinal examination using indirect ophthalmoscopy, cycloplegic refraction, visual acuity testing, visual field assessment, and color vision assessment. These results have been confirmed in 26 additional children, by dilated retinal examination with indirect ophthalmoscopy (4,5). The normal ERG results reported by Cimaz and colleagues thus reinforce the findings of previous studies.

We have also performed ERG in infants born to mothers who had been treated with HCQ during pregnancy (Table 1). All 4 mothers had systemic lupus erythematosus. HCQ treatment was continued throughout gestation (n = 4) and breast-feeding (n = 2). The mean gestational age of these children was 38.6 weeks (range 38–39), and the mean weight at

**Table 1.** Characteristics of the study infants and exposure to HCQ in utero\*

Patient	Age, months/ sex†	Gestational age, weeks	Neonatal weight, gm	Apgar score, at 1 minute/ 5 minutes	Maternal diagnosis	Age of mother at delivery, years	HCQ exposure in mother‡	
							Continuous duration, months	Total cumulative dose, gm
1	4/F	39	3,320	10/10	SLE	23	22	264
2	13/F	39	3,000	10/10	SLE	30	84	1,008
3	6/F	38	2,330	7/10	SLE	30	98	1,176
4	7/F	38.5	2,630	10/10	SLE	32	74	888

\* HCQ = hydroxychloroquine; SLE = systemic lupus erythematosus.

† Age at which electroretinography was performed.

‡ Exposure before delivery.

birth was 2,820 gm (range 2,330–3,320). Ophthalmologic evaluation included dilated retinal examination using indirect ophthalmoscopy and ERG. The median age of the children at the time of ERG was 6.5 months (range 4–13). No abnormalities were found.

Interestingly, Cimaz and colleagues emphasized that 5 of the 6 children they studied were breast-fed. We have previously analyzed HCQ in the breast milk of 2 mothers (6); the HCQ concentrations were 344 ng/ml and 1,424 ng/ml, respectively. We later confirmed these results in 2 more mothers, whose breast milk HCQ concentrations were 1,131 ng/ml and 1,392 ng/ml. It can thus be calculated that the HCQ ingestion by the infants was no more than 0.2 mg/kg/day. These levels are concordant with the daily ingestion of 0.11 mg/kg in 1 infant reported by Nation et al (7). The amount of HCQ received by children throughout lactation is very small compared with the daily therapeutic dosage (6.5 mg/kg in adults) (8). Additionally, given that HCQ concentrations in breast milk are low compared with those found in cord blood (transplacental passage), it does not seem logical to advise against breast-feeding if HCQ therapy has been maintained throughout pregnancy.

Taken altogether, these data provide support for previous evidence of the safety of HCQ during pregnancy and lactation and are concordant with the experience of selected experts, as reported in a national survey concerning the use of antimalarial drugs in lupus pregnancy (9). None of the respondents reported having seen any fetal toxicity related to the use of antimalarial agents.

However, since retinal toxicity of HCQ in adults is rare (3), the number of children studied may be insufficient to detect infrequent fetal retinal toxicity. A multicenter study including complete ophthalmologic examinations and long-term followup of the children would be recommended in order to obtain more definitive answers.

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### **Elective pregnancy termination and microchimerism: comment on the article by Khosrotehrani et al**

*To the Editor:*

In continuation of the intriguing microchimerism story, Khosrotehrani et al (1) make the point that it is during early pregnancy when fetal loss is most likely to result in the release of progenitor cells, those cells that have the greatest potential for engraftment, expansion, and differentiation within maternal tissues. I would like to emphasize that elective termination of pregnancy is unique in terms of the release of these progenitor cells as well as facilitating their access to the maternal circulation.

There is a major difference between a spontaneous miscarriage and elective termination of pregnancy. In the very early months of pregnancy, the expulsion accompanying spontaneous miscarriage is nearly always preceded by the death of the embryo or fetus (2). Any fetomaternal cell trafficking that occurs is, for the most part, between the mother and dead cells. In contrast, during elective termination, a live healthy fetus is torn from the uterine lining, producing breaches and bleeding. The maternal blood is exposed to a profusion of live undifferentiated cells deriving from the torn and macerated tissues of the live fetus. Analysis by quantitative polymerase chain reaction amplification demonstrates a large fetal–maternal transfusion (3). Because engraftment is directly related to the size, viability, and lack of differentiation of the fetal cellular inoculum, engraftment is far more likely to follow elective termination of pregnancy than spontaneous miscarriage. With term delivery, as pointed out by the authors, there is blood exchange, but the cells are well differentiated, posing little threat of engraftment.

The authors' plea that physicians obtain detailed pregnancy histories in women with scleroderma or other diseases possibly related to microchimerism (4,5) is judicious. In fact, a thorough pregnancy history, looking in particular for elective termination of pregnancies, may be advisable in all women, because the effects of a large fetal–maternal transfusion of engraftment-prone cells on the development or expression of virtually any disorder are at this time unknown.

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### Reply

*To the Editor:*

We thank Dr. McGrath for his insightful comments. In our study, we analyzed the association between fetal cell microchimerism, defined by the persistence of male fetal cells in women after pregnancy, and several pregnancy-related variables. We observed a significant association between fetal loss, defined as both spontaneous abortion or elective termination, and microchimerism. Most of the studies included in our meta-analysis did not distinguish between spontaneous abortions or elective termination. Therefore, we could not analyze these 2 entities separately and do not have any data at present to strengthen Dr. McGrath's hypothesis.

In his comments, Dr. McGrath made the interesting suggestion that spontaneous abortion with preceding fetal death may not be a source of fetal cell microchimerism. Conversely, elective termination, as we have previously shown by quantitative polymerase chain reaction analysis, results in a large transfer of fetal nucleated cells into the maternal circulation (1). We agree with Dr. McGrath that the frequency of pregnancy-associated progenitor cells is likely to be higher in early gestation, and that the transfer of fetal progenitor cells is important for the long-term development of microchimerism.

However, recent reports have described the detection of fetal cell microchimerism in 30–50% of healthy women (2). Spontaneous abortion (including early pregnancy loss, defined as the loss of an embryo before the clinical diagnosis of pregnancy) occurs in 32% of all conceptions in healthy young nulliparous women (3). Given the high and somewhat similar frequencies of microchimerism and spontaneous miscarriage in women, we cannot exclude the possibility that fetal cells from a spontaneous miscarriage contribute to the development of microchimerism. Further research should address the question as to whether there is a difference in the development of fetal cell microchimerism following spontaneous abortion versus elective termination.

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### Causes of familial aggregation of fibromyalgia: comment on the article by Arnold et al

*To the Editor:*

We read with interest the report by Arnold et al on familial aggregation of fibromyalgia (FM) (1). Although we tend to agree with the authors' statement that their finding of familial aggregation of FM supports the validity of the diagnosis, there should be at least 2 caveats with regard to their further contention that the finding of familial aggregation also supports the notion of a genetic etiology.

First, the increased odds ratio for FM among first-degree relatives of index patients could reflect similar intrauterine conditions among siblings. It is established that components of the hypothalamic–pituitary–adrenal axis, such as corticotropin-releasing hormone, which is responsible for the human stress reaction, can cross the placenta and may have deleterious effects that manifest many years after birth (2,3). Since this axis is considered to be dysfunctional in FM, it is not inconceivable that intrauterine development of siblings born to a mother with a high level of stress may predispose such siblings to the eventual development of FM, quite independent of any genetic determinant.

Second, it is important to point out that to the extent that FM is describable in terms of a somatization-like disorder (4), environmental and behavioral influences may be of prime importance. Specifically, the “language of the body” (5), or the use of somatic symptoms as a means by which to express anguish, to acquire attention, or to deal with anxiety and guilt, are all pathologic forms of expression that may be learned within a family context, thus increasing the likelihood of FM occurring in more than one member of a family.

Viewed in this context, Arnold and colleagues' findings are indeed intriguing, but multifactorial causation, or conceivably a combination of genetic predisposition and a summation of life events (similar to the elegant model recently suggested for depression, linking life events with a polymorphism in the serotonin transporter gene [6]), better serve to explain these findings than do genetics alone.

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## Reply

### *To the Editor:*

We welcome the comments of Drs. Ablin and Aloush, which provide us with an opportunity to clarify 2 issues. First, we did not claim in our article that genetics alone causes fibromyalgia. Indeed, we agree that environmental factors very likely play a role. Second, we agree that familial aggregation can be due to either shared familial environmental factors, genetic factors, or a combination of the 2.

However, the high degree of familial aggregation found in our study (an odds ratio or hazard ratio of 5.8–8.5, depending on the type of analysis) cannot be plausibly explained in the absence of genetic factors. For example, consider an analysis by Khoury and colleagues (Khoury MJ, Beaty TH, Liang KY. Can familial aggregation of disease be explained by familial aggregation of environmental risk factors? *Am J Epidemiol* 1988;127:674–83): if one makes the unrealistic assumption of complete correlation of exposure to an environmental risk factor among relatives, and then further

assumes that the environmental risk factor has a relative risk for disease of 10—an extraordinarily high effect—one would still obtain only modest levels of familial aggregation (relative risk <2.0) in the absence of genetic effects. Similarly, Guo has shown that even under the slightly more realistic, but still unlikely, scenario of 2 environmental risk factors, each with a correlation of 0.5 among relatives and with a relative risk of disease of 5, acting multiplicatively, the relative risk for familial aggregation in the absence of genetic effects is still only 2 (Guo M. Familial aggregation of environmental risk factors and familial aggregation of disease. *Am J Epidemiol* 2000;151:1121–31). If we return to our study and convert our estimates from odds ratios and hazard ratios to relative risk measures, these are all 5 or greater—effect sizes that are unachievable under any realistic scenario in the absence of any genetic influence. Therefore, it is not plausible that shared intrauterine conditions (see Khoury and colleagues' discussion of teratogens) or patterns of pathologic expression learned within families could account entirely for the high level of familial aggregation observed—unless these factors themselves were strongly determined by genetics.

In conclusion, while not precluding a potentially important role of environmental factors, our findings strongly suggest that genetic factors contribute to the causation of fibromyalgia, and it will be important to search for such factors in subsequent studies.

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