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# LETTERS

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## Evidence for interaction between disease severity and comorbidity in rheumatoid arthritis? comment on the article by Navarro-Cano et al

*To the Editor:*

Navarro-Cano et al are to be congratulated on their elegant study demonstrating the independent effects of disease severity and comorbidity on rheumatoid arthritis (RA) mortality (Navarro-Cano G, del Rincón I, Pogosian S, Roldàn JF, Escalante A. Association of mortality with disease severity in rheumatoid arthritis, independent of comorbidity. Arthritis Rheum 2003;48:2425–33). I am only curious about one aspect they do not report: was there any evidence for interaction between these 2 factors?

It is tempting to speculate that the excess mortality in RA could be, in part, explained by such an interaction, especially as regards cardiovascular comorbidity. We should, of course, be aware that detecting main effects is always easier than detecting interaction, but it would be interesting to learn the results of such an analysis in this data set.

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## Signs of systemic disease are strong determinants of mortality in rheumatoid arthritis: comment on the article by Navarro-Cano et al

*To the Editor:*

We read with interest the recent report by Navarro-Cano et al on disease severity, comorbidity, and survival in rheumatoid arthritis (RA) (1). Their analysis of a clinic-based cohort of consecutive patients with RA demonstrates that general measures of RA disease severity, including the RA component of the Duke Severity of Illness Checklist, are associated with mortality in patients with RA independently of measures of comorbidity. They speculate that severe RA could mask the recognition of comorbid conditions associated with mortality, or that severe RA could be associated with conditions that cause sudden, unexpected death. Given the recent developments in the understanding of the pathogenesis of RA and the emergence of new, more specific treatment strategies, it would be of interest to further define the underlying mechanisms behind these relationships.

A number of studies have demonstrated an association between extraarticular disease manifestations in RA and mortality (2–4). We recently studied the epidemiology of extraarticular disease in RA and its impact on survival in a study of a community-based RA cohort that extended over 46 years (5,6). Severe extraarticular manifestations, identified according to predefined criteria (4), were associated with an increased mortality, whereas patients with RA without extraarticular disease had a survival similar to that of the general population (5). In multivariate models, the association between extraarticular manifestations and mortality was independent of comorbid conditions, defined using the Charlson Comorbidity Index. Overall, extraarticular RA was the strongest determinant of mortality studied (5,6).

The findings by Navarro-Cano et al do not contradict these results, because different measures of disease severity are likely to correlate to a certain extent. It is unfortunate that Navarro-Cano et al do not provide data on severe extraarticular disease manifestations among their patients. Their measures of disease severity rely mainly on joint deformation and disability. They wonder how the severity of RA could lead to an increased mortality risk in a manner independent of comorbidity, and suggest that excess allostatic load in patients with RA may contribute to poor survival (1). We propose that disease-related manifestations, including classic extraarticular disease as well as the cardiovascular disease burden, which increasingly is being identified as a complication of RA in itself, are the principal contributors to premature mortality.

Available data on extraarticular RA and mortality are more compatible with a specific association between pathogenic factors in extraarticular manifestations and fatal disease. Suggested shared disease mechanisms in extraarticular RA and coronary artery disease include clonally expanded CD4+ T cells with cytotoxic capabilities (7) and systemic endothelial activation (8). Future studies should aim at clarifying the role of these and other factors in determining mortality in patients with RA. We suggest that signs of systemic disease activity are the strongest determinants of mortality, and, more than the extent of joint disease, are the true measures of disease severity in RA. Studies of survival in patients with RA should include data on severe extraarticular disease manifestations. If such data are not available, the authors should at least discuss their results in the context of the known strong association between extraarticular RA and excess mortality.

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## Reply

*To the Editor:*

We thank Dr. Boers and Drs. Turesson and Matteson for their interest in our study. To address Dr. Boers' question, we tested the effect of adding a COMDUSOI × RADUSOI (non-RA and RA components of the Duke Severity of Illness Checklist, respectively) interaction term to a Cox proportional hazards model that also included age, sex, RA duration, COMDUSOI, and RADUSOI as independent variables, and time to death within 6 years as the outcome (i.e., Model 1 in Table 3 of our article). The product term increased the model's likelihood ratio (LR) chi-square from 126.7 to 131.7 ($P$ = 0.03), providing evidence of a statistically significant interaction between comorbidity and disease severity. To interpret this interaction, we graphed the age-, sex-, and RA duration–adjusted probability of death during 6 years of observation, according to the COMDUSOI and RADUSOI categories shown in Figure 1. The top graph shows the mortality associated with each comorbidity level, for each of the disease severity categories. Greater levels of comorbidity were associated with greater mortality in each of the severity levels, but the slope of the increase was highest when the severity was greater. It is also informative to view the same data after shifting the axes, with RA severity on the abscissa, as shown in the middle graph. Here, different levels of disease severity were associated with small differences in 6-year mortality when the comorbid burden was low, but when comorbidity was high, disease severity markedly increased mortality. These data suggest synergism between comorbidity and severity in increasing mortality in RA.

Drs. Turesson and Matteson suggest that systemic disease activity, not joint disease, is the true measure of disease severity in RA. It may help to consider that the 2 processes are not necessarily separate. The extent of joint damage in RA is strongly related to past systemic disease activity, integrated over time. Thus, an association between joint damage and mortality may also be evidence of a link between systemic disease activity and mortality in RA. It should also be noted that the RA disease severity measures we used were not based on any single variable, but rather on an overall evaluation of the patient's symptoms, signs, laboratory features, expected response to treatment, and prognosis. Within this framework, the presence or absence of subcutaneous nodules, the most

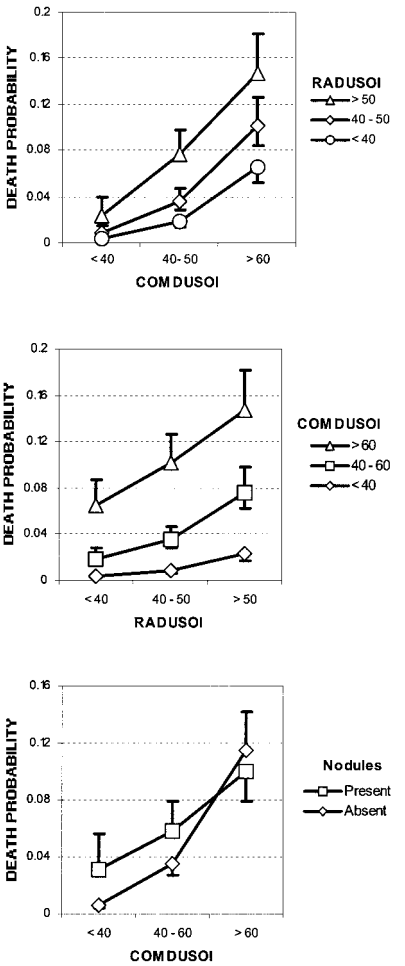


**Figure 1.** **Top** and **middle,** Age-, sex-, and disease duration–adjusted probabilities of death over 6 years, according to the rheumatoid arthritis (RA) Duke Severity of Illness Checklist (RADUSOI) and non-RA DUSOI (COMDUSOI) levels. **Bottom**, Adjusted probability of death according to COMDUSOI and the presence of nodules ($P$ for interaction term = 0.05). Bars show the SEM.

frequent extraarticular feature of RA, explained ~6% of the variance in the RADUSOI, and 7% in the RA severity scale.

As Drs. Turesson and Matteson have reported, extraarticular RA and comorbid conditions appear to independently raise the risk of death in RA. However, the extent to which comorbidity and extraarticular RA modify each other's effect on survival (i.e., the extent to which the 2 variables interact) has not been explicitly tested. Here, too, we can provide estimates, by testing the interaction between comorbidity and subcutaneous nodules. We substituted subcutaneous nodules for the RADUSOI in the Cox regression models described above. In the uninteracted model, which had a LR chi-square of 123.2 with 5 degrees of freedom (for age, sex, RA duration, COMDUSOI, and nodules), the presence or absence of nodules was not significantly associated with mortality. However, when a nodules × COMDUSOI product term was

added to the model, the LR chi-square increased to 126.9 ($P = 0.05$), suggesting an interaction of borderline statistical significance between the 2 variables. The bottom graph in Figure 1 shows the age-, sex-, and RA duration–adjusted 6-year probability of death, according to COMDUSOI level and the presence of nodules.

The effect of subcutaneous nodules on vital status at 6 years depends on the level of comorbidity. At low to moderate comorbidity levels (COMDUSOI $\leq$60), subcutaneous nodules appear to raise the risk of death, but this effect is lost in the highest comorbidity level. Our interpretation is that extraarticular RA, defined as the presence or absence of subcutaneous nodules, may be a factor associated with death in RA, but that its effect is overcome by concurrent illnesses, when these are severe. This does not exclude the possibility that more severe extraarticular RA may behave differently with respect to comorbidity, perhaps in a manner similar to that of the RADUSOI.

We thank Dr. Boers and Drs. Turesson and Matteson for prompting us with their questions to explore these interactions in our data.

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## Prospective comparison of sodium hyaluronate and hylan G-F 20 in a clinical practice: comment on the concise communication by Martens

*To the Editor:*

A report by Martens (1) and a comment on it by Gil et al (2) have added to the growing anecdotal evidence for a difference in safety profiles between available hyaluronan products such as Hyalgan (sodium hyaluronate; Fidia SpA, Padua, Italy) and Synvisc (hylan G-F 20; Genzyme Biosurgery, Ridgefield, NJ). Because there have been few head-to-head studies to aid in making a decision on the use of one product over the other, we undertook a prospective, controlled trial, approved by the local ethics committee, to evaluate the safety and efficacy of Hyalgan and Synvisc in knee osteoarthritis patients in an orthopedic practice.

The protocol called for the assignment of 100 patients to receive intraarticular treatment with Hyalgan or Synvisc (50 patients per treatment arm), based on the consultant to whom the patient was referred, with followups scheduled at 6 weeks and 6 months from the day of first injection. The planned efficacy outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index scores for pain and function (3). Safety and tolerability were evaluated as complications or adverse events noted by senior house officers. Weekly injections were to be given as described in the prescribing information for the respective agent (5 weekly injections for Hyalgan and 3 for Synvisc). Injections were given either by the assessors or by an experienced nurse practitioner. The study was unblinded. Comparison of baseline disease and demographic characteristics showed no apparent differences between treatment groups.

Approximately 6 months after initiation of the trial, it was noted that 6 of 29 patients treated with Synvisc had developed complications resembling those in Synvisc-treated patients described by Martens and other investigators (1,4–7). Patients were presenting with acutely hot, painful, swollen knees, with a clinical picture resembling that of septic arthritis. In 5 of 6 patients, the reaction occurred after the second of the planned 3-injection course. Four of the patients were admitted for arthrocentesis, but the clinical pattern was subsequently recognized and the patients returned home without undergoing arthrocentesis. The symptoms were alleviated in ~4 days, with rest, ice, and oral antiinflammatory medication. No crystals were seen on microscopy of aspirated fluid, cultures were negative, and a high cellular infiltrate with a predominance of neutrophils was seen. No such complications occurred in any of 25 Hyalgan-treated patients. Based on comparisons of proportions analysis with 95% confidence intervals, 6 of 29 patients with reactions (in the Synvisc group) represented a significantly higher proportion compared with 0 of 25 patients with reactions (in the Hyalgan group) ($P = 0.009$). There were no other documented adverse reactions in either group. An intermediate assessment of efficacy did not suggest a benefit of the Synvisc over Hyalgan. Therefore, the study was terminated based on ethical grounds, prior to enrollment of 100 patients as had been called for in the protocol.

Consistent with descriptions previously reported in the literature (1,2,4–8), the reactions 1) generally occurred after at least 2 injections had been given, 2) occurred within 72 hours of an injection; 3) were similar to clinical findings in septic arthritis but with negative results on synovial fluid culture, an absence of crystals, and presence of elevated cellular infiltrate; and 4) generally required intervention. Based on a literature search (Medline, Toxline, EMBase, International Pharmaceutical Abstracts, and Biosis), Hyalgan has not been associated with reports of pseudoseptic reactions. The basis for these reactions to Synvisc has not been determined, but preclinical and clinical data suggest that they may represent an immune response to a component of the hylan G-F 20. One patient who experienced a pseudoseptic reaction was found to have serum antibodies to chicken proteins and hylan, but not to hyaluronan (5). The study reported by Bucher et al (9) showed that rabbits immunized with Synvisc—but not those immunized with Hyalgan—produced antibodies to chicken proteins or hyaluronan.

One recent report describes a head-to-head comparison between Synvisc, another native hyaluronan preparation (Artzal [sodium hyaluronate; Astra Läkemedel, Södertälje, Sweden]), and placebo (10). Although there were no treatment-attributed safety reactions, a relatively high number of serious adverse events occurred in all treatment groups, some of which were attributed to the underlying disease. Since no details of these events were provided, it is difficult to ascertain whether any might have resembled pseudoseptic reactions. Our experience, combined with published data, suggests that hylan G-F 20 may present a unique safety risk. While this reaction does not appear to have immediate serious clinical consequences, possible long-term consequences of

fulminant inflammatory reactions in a diseased knee are worrisome and await further study.

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## Reply

*To the Editor:*

The results of Brown and colleagues' head-to-head prospective study of hylan G-F 20 and sodium hyaluronate suggests that hylan G-F 20, a high molecular weight, crosslinked hyaluronic acid preparation, results in more spontaneous acute inflammatory reactions than does sodium hyaluronate. A relatively high frequency of spontaneous acute inflammatory reactions (SAIRs) in patients treated with hylan G-F 20 has been suggested in case reports and series (Puttick MP, Wade JP, Chalmers A, Connell DG, Rangno KK. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. J Rheumatol 1995;22:1311–4), but not demonstrated and quantified in a prospective manner as has been done by Brown et al. The authors cite another study in which adverse reactions to both hylan G-F 20 and another native high molecular weight hyaluronan preparation occurred, but report that detailed information on adverse events was not presented. A report of 1 large study of sodium hyaluronate injection noted 1 possible SAIR among 105 patients randomized to receive sodium hyaluronate, but again detailed synovial fluid results were not presented (Altman RD, Moskowitz R, and the Hyalgan Study Group. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. J Rheumatol 1998;25:2203–12). Clearly, hylan G-F 20 can cause SAIRs when given repeatedly, and other hyaluronans might as well; a prospective study of repeated injection of sodium hyaluronate, with adequate patient numbers and injections, would help answer this question.

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## Role of anti–glial fibrillary acidic protein antibodies in the pathogenesis of neuropsychiatric systemic lupus erythematosus should be clarified: comment on the article by Trysberg et al

*To the Editor:*

We read with interest the recent report by Trysberg et al (1). The authors are the first investigators to describe increased levels of 2 products of neuronal and astrocytic degradation, the neurofilament triplet protein (NFL) and glial fibrillary acidic protein (GFAP), in the cerebrospinal fluid (CSF) of patients with neuropsychiatric systemic lupus erythematosus (NPSLE). Moreover, successful therapy with cyclophosphamide in 6 patients with NPSLE resulted in significantly decreased CSF levels of both proteins. The authors suggested a role for NFL and GFAP as biochemical markers of brain damage in patients with NPSLE.

These results may be of particular interest in view of the finding of serum anti-GFAP antibodies in SLE patients (2). In fact, Sanna and coworkers showed a correlation between serum anti-GFAP antibodies and the neuropsychiatric disturbances in patients with SLE (2). We recently investigated the prevalence of anti-GFAP antibodies in 51 unselected SLE outpatients (44 women, 7 men; mean age 36.8 years [range 22–54 years]; mean disease duration 9.4 years [range 0.5–26 years]) attending the division of rheumatology of Policlinico Umberto I, Università di Roma "La Sapienza." In this cohort, we found a prevalence of anti-GFAP antibodies of 15.7% (8 of

51 patients), without any correlation between anti-GFAP antibodies and neuropsychiatric morbidity (Alessandri C, et al: unpublished observations). Nevertheless, previous studies have demonstrated elevated levels of antineuronal antibodies in the CSF from patients with NPSLE (3–5), and a case report has described the presence of anti-GFAP antibodies in the serum and CSF from a patient with SLE who had headache and anosmia (5). Access of autoantibodies to the nervous system may occur through a disrupted blood–brain barrier or through de novo synthesis in the nervous system (for review, see ref. 6).

Taken together, these findings suggest that the role of anti-GFAP antibodies in the pathogenesis of NPSLE should be clarified by prospective studies using both intrathecal and serum determinations.

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## Reply

*To the Editor:*

We appreciate the opportunity to comment on the letter from Alessandri and colleagues regarding our recent article. A recent study (Sanna G, Piga M, Terryberry JW, Peltz MT, Giagheddu S, Satta L, et al. Central nervous system involvement in systemic lupus erythematosus: cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. Lupus 2000:9:573–83) showed antibody activities to GFAP in a limited number of sera from patients with SLE, especially those displaying signs of CNS lupus.

Although a disrupted blood–brain barrier is not common in CNS lupus (with the important exception of stroke due to the antiphospholipid antibody syndrome), B cell activation within or outside the CNS might give rise to either brain tissue antigen-specific (less likely?) or polyclonal B cell responses. Such an activation might, irrespective of the initiating event, trigger glial-specific antibody production. The issue of whether the GFAP antibodies found are triggered by antigen-specific or mitogenic responses may be tested experimentally, e.g., by combining antibody analyses with specific antigen analyses.

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## Use of novel elution regimens of autoantibodies in lupus kidneys: comment on the article by Xie et al

*To the Editor:*

In a recent article, Xie et al compared the recovery of antibodies from renal cortex of mice with lupus using a 0.15*M* glycine-HCl buffer, 1.3*M* ammonia thiocyanate/0.15*M* glycine-HCl buffer, or 5*M* urea/0.15*M* glycine-HCl, all at pH 2.8 (1). The yield of IgG and tested autoantibodies was significantly higher in the extract obtained with the solution containing urea. IgG autoantibodies to double-stranded DNA were the most prevalent autoantibodies recovered from the mouse kidneys. These autoantibodies and other detected autoantibodies, however, did not add up to more than approximately half of the total IgG recovered per 100 mg of renal cortex, as judged from the text and figures. What other autoantibodies might have been present and were not analyzed by the authors? It would have been informative to add the recovered IgG antibodies for each studied mouse to determine the percentage of IgG accounted for by the tested antibodies. Of note is that in a recent study of kidneys from patients with systemic lupus erythematosus, the specificity of the majority of recovered IgG was also not established (2).

The authors claimed that the use of urea was a novel elution regimen compared with the prior use of milder elution conditions. Previous studies with mouse and human kidney specimens have used even a stronger perturbant, namely 6*M* guanidine hydrochloride, to dissociate antigen–antibody bonds (2–4). The authors reported a 0–25% loss of antibody activity when 5*M* urea was used in the eluting buffer (1). This most likely resulted from cleavage of disulfide bonds in the unfolded antibody molecules in urea, by a disulfide exchange reaction. This could have been prevented by the use of 0.1 m*M* iodoacetamide in the elution buffer to block free sulfhydryl groups.

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and other macromolecules in murine renal glomeruli. Clin Exp Immunol 1996;103:285–8.
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## Reply

*To the Editor:*

We thank Dr. Mannik for the thoughtful feedback. He is right in pointing out that the eluted anti-DNA antibodies did not add up to the total Ig that was eluted. Currently, we do not know whether other autospecificities might also have been represented in the "total" eluates, and this clearly warrants further investigation. We would also like to thank Dr. Mannik for the suggestion for improvement of the elution buffer through the addition of iodoacetamide.

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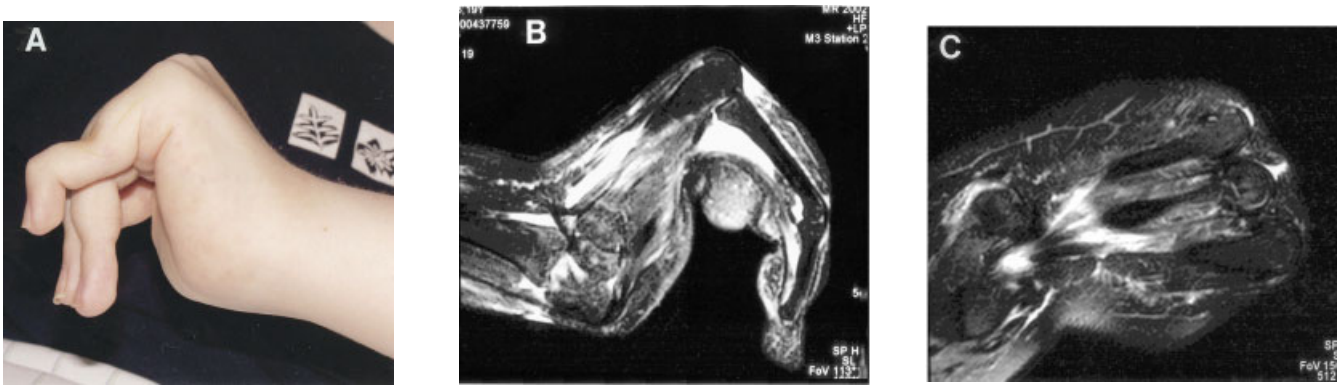
## *Clinical Images: Periarticular inflammation in rapidly developing Jaccoud's arthropathy*




The patient first presented to our department at the age of 19 years, with a 6-month history of arthritic symptoms in her wrists, fingers, and toes. Only a few weeks after the initial occurrence of these symptoms, a massive deforming arthropathy with flexion contractures had developed (**A**). At the time of presentation at our clinic, she had renal involvement (proteinuria, hematuria, renal insufficiency), cerebral involvement (migraine headaches, anxiety, ischemic lesions seen on magnetic resonance imaging [MRI]), thrombocytopenia, positive lupus anticoagulant, and other laboratory findings characteristic of systemic lupus erythematosus (SLE). Because of the extremely rapid development of deforming Jaccoud's arthropathy, MRI of the hands was performed. Besides the typical deformities without erosive changes, increased signal intensity (T2-weighted, fat-suppressed images) was demonstrated in various joint capsules and tendon sheaths of the hand (**B** and **C**). This was mainly caused by effusions, since after administration of gadolinium, nearly no enhancement could be demonstrated on T2-weighted, fat-suppressed images. This confirms the notion that Jaccoud's arthropathy in SLE is caused by periarticular inflammation rather than true arthritis.

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