Effect of gold treatment on cytokine expression in synovium

A recent paper in this journal described the effect of intramuscular gold treatment on cytokine expression in synovial membranes from patients with rheumatoid arthritis. In that paper, the authors described changes in synovial membrane expression of interleukins (IL)-1α, IL-1β, IL-6, and tumour necrosis factor α in patients who had received intramuscular gold treatment. However, the authors failed to mention that some of the results had been published in another journal by a similar group of authors. Neither paper is cross referenced to the other, and it is not clear from these two papers whether the authors are reporting the same set of results in two different papers.

In one paper, the authors described a significant failure rate with blind needle biopsy of the synovial membrane, which is particularly a problem with studies involving sequential biopsy as was performed in these two studies. Our experience is similar with this technique and we have now changed to performing all synovial biopsy under direct vision through a needle arthroscopy under local anaesthesia. However, despite the fact that the two patient groups appear to be similar, if not identical, in these two reports, one paper states that only seven of 18 patients recruited in the study gave three satisfactory sequential synovial biopsy specimens, while the other paper implies, though not clearly stated, that satisfactory synovial biopsy specimens were obtained in all 10 patients for all time points (0, 2, and 12 weeks). This suggests either that the authors’ biopsy technique or success rate has changed dramatically during the period between preparation of the two papers, or that additional patients were obtained to ‘make up the numbers’.

Could the authors please confirm whether:

1. The patients studied in these two papers are, in fact, identical.
2. The same results for IL-1β have been published in two different papers in two different journals.
3. All the patients reported in one paper provide adequate synovial biopsy specimens for all three time points and, if so, how was this possible in view of the results and discussion in the other paper from the same group.

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Cytoplastic staining, ANA negative status, and ENA testing in rheumatic diseases

Koh and colleagues reported cytoplastic immunofluorescence staining on HEP-2 cells in 75 of 1173 sera (6.4%) of patients with various rheumatic diseases referred to the Royal National Hospital for Rheumatic Diseases in Bath. Forty two of these 75 sera (56%) were antinuclear antibody (ANA) positive, and 33 ANA negative. Ten of the 75 sera (13.3%) were extractable nuclear antigen (ENA) positive by immunodiffusion (mainly SS-A and Jo-1) and five of these 10 sera were ANA negative. No association of cytoplastic staining patterns with any specific disease was observed. However, because five of the 10 ENA positive sera were ANA negative, the authors concluded that ‘cytoplastic staining should not be ignored as it may indicate the presence of antibodies to ENA in the absence of nuclear staining’.

We wish to question whether this conclusion is strong enough to advocate positive cytoplastic staining as an indication for further routine testing for ENA in ANA negative patients with rheumatic diseases. In our laboratory, 5843 sera of patients with various rheumatic diseases were tested for ANA on HEP-2 cells in the past two years. Six hundred sera (10.3%) showed cytoplastic staining, which is comparable to the 6.4% in Bath. Two hundred and ninety five of those 600 sera with cytoplastic staining were randomly tested further for ENA by immunodiffusion: 32 (10.8%) were ENA positive (mainly SS-A and SS-B), which is similar to the 13.3% in Bath.

Of the 600 sera with cytoplastic staining, 179 were ANA positive (29.8%). This percentage is clearly less than that observed in Bath (56%). Theoretically, this discrepancy could be attributable to the study of different patient groups, but the frequency of separate diagnoses did not differ much: systemic lupus erythematosus 12% in Bath vs 10% in Amsterdam; Sjogren syndrome 6% vs 4%; scleroderma 4% vs 1%; rheumatoid arthritis 12% vs 17%. These data indicate that the Bath and Amsterdam patient groups are quite similar.

Although we routinely cascade testing stops with a negative ANA, 171 ANA negative sera, randomly selected for quality control reasons, were tested for ENA. Of these sera, 152 (89%) did not show any cytoplastic staining. None of the sera that were ANA negative were shown by a kind of negative sera which showed a cytoplastic staining was ENA positive, which is in contrast to the results in Bath, where five of 33 ANA negative sera were cytoplastic positive.

We conclude that it is not useful routinely to follow cytoplastic staining in HEP-2 cells in the absence of ANA by ENA testing in daily practice for rheumatic patients, because a) ENA positive sera also occur among ANA negative sera without cytoplastic staining, and b) the prevalence of positive ENA in ANA negative sera with cytoplastic staining is rather low: none of 19 in Amsterdam, five of 33 in Bath.

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Authors’ reply

Further to our data, Dr Lems and colleagues provide evidence that a positive anti-ENA may occur in sera that are negative for anti-cytosplastic and for nucleocytobodies on routine indirect immunofluorescence of HEP-2 cells. We have not tested a sufficient number of such sera ourselves to assess the relative chance of detecting a positive ENA in the absence of nuclear or cytoplasmic staining. However, we still maintain that cytoplastic staining may indicate the presence of anti-ENA, especially considering the predominantly cytoplastic distribution of autoantigens such as Jo-1 (histidyl-RNA) and SS-A, three. Perhaps the most important feature for clinicians is that a negative ANA on immunofluorescence should not preclude further serological testing for autoantibodies when clinically indicated.

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