LETTERS

Effects of gold on interleukin-2 and interleukin-2 receptor: comment on the article by Sfikakis et al

To the Editor:

In their interesting paper, Sfikakis et al state "no previous study, to our knowledge, has investigated the in vitro effects of gold compounds on the IL-2/IL-2R [interleukin-2/interleukin-2 receptor] system" (1). This is an oversight, since my colleagues and I have previously shown an in vitro effect of gold sodium thiomalate (GST) on the IL-2/IL-2R system (2). In our experiments, GST inhibited the expression of Tac antigen on phytohemagglutinin-stimulated human T cells. GST also inhibited the proliferative response of T cells to IL-2; this inhibitory effect could be observed even when GST was added after maximum expression of Tac antigens had occurred (2). These observations confirmed those of Wolf and Hall (3), and are complementary to those of Sfikakis and coworkers (1). Gold compounds, therefore inhibit lymphocyte responses to IL-2, and the biosynthesis of IL-2 and IL-2R. The work of Sfikakis et al shows that this inhibition of biosynthesis occurs, at least in part, at the transcription stage.

One criticism of all laboratory work in this area, including ours, is that the concentration of gold to which lymphocytes are exposed (as opposed to the concentration of gold per milliliter of culture medium) is 15-30 fold higher than that which is likely to be found in blood or synovial fluid. This is only one of many variables that must be considered before an in vitro phenomenon could be assumed to occur in the gold-treated patient.

Manfred Harth, MD, FRCPC
University of Western Ontario
London, Ontario, Canada

Reply

To the Editor:

We read with interest the article by Drosos et al showing that rheumatoid arthritis (RA) is less severe in Greek than in British patients (Drosos AA, Lanchbury JS, Panayi GS, Moutsopoulos HM: Rheumatoid arthritis in Greek and British patients: a comparative clinical, radiologic, and serologic study. Arthritis Rheum 35:745-748, 1992). Interestingly, in 1987 we carried out a similar study, comparing characteristics of 63 patients from the same British hospital involved in the study by Drosos (Guy's Hospital, London) with 63 patients followed up at the Alicante General Hospital in Spain, and we also found that British patients seemed to have more severe disease.

In each group, all 63 patients fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for RA (Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA Jr, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315-324, 1988). All patients in both institutions were evaluated by the same investigator (ER) according to a protocol which included a medical receptor biosynthesis at the messenger RNA (mRNA) level by gold compounds has not been demonstrated previously.

In our experiments, the lowest concentrations of gold compounds used (2 µg of GST [i.e., 10-fold lower than that used by Harth and colleagues] and 0.1 µg of auranofin per ml of culture medium) caused substantial decreases of 20% and 75% in the accumulation of IL-2 mRNA, as well as decreases of 38% and 58% in the accumulation of IL-2 receptor mRNA, in phytohemagglutinin-stimulated peripheral blood mononuclear cells. According to published data, the gold levels that are attained in the serum of GST- and auranofin-treated patients are in the range of 2-5 µg/ml and 0.3-1.0 µg/ml, respectively (for review, see refs. 3 and 4); these concentrations are equivalent to the gold in 4-10 µg/ml of GST and in 0.9-3 µg/ml of auranofin.

P. P. Sfikakis, MD
Athens University Medical School
Athens, Greece
P. Panayotidis, MD
Royal Free Hospital
London, UK


Differences between Spanish and British patients in the severity of rheumatoid arthritis: comment on the article by Drosos et al

To the Editor:

We read with interest the article by Drosos et al showing that rheumatoid arthritis (RA) is less severe in Greek than in British patients (Drosos AA, Lanchbury JS, Panayi GS, Moutsopoulos HM: Rheumatoid arthritis in Greek and British patients: a comparative clinical, radiologic, and serologic study. Arthritis Rheum 35:745-748, 1992). Interestingly, in 1987 we carried out a similar study, comparing characteristics of 63 patients from the same British hospital involved in the study by Drosos (Guy's Hospital, London) with 63 patients followed up at the Alicante General Hospital in Spain, and we also found that British patients seemed to have more severe disease.

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Table 1. Characteristics of rheumatoid arthritis in 63 British and 63 Spanish patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>British Patients</th>
<th>Spanish Patients</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness</td>
<td>53</td>
<td>42</td>
<td>2.65 (1.05–6.82)</td>
</tr>
<tr>
<td>Extraarticular manifestations</td>
<td>26</td>
<td>11</td>
<td>2.99 (1.25–7.24)</td>
</tr>
<tr>
<td>Rheumatoid Nodules</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Values are the number of patients. Some patients had more than 1 extraarticular manifestation.

history and general clinical evaluation, with special attention paid to extraarticular manifestations and the articular examination. Although there was some difference in age between the groups (mean ± SD 61 ± 13 years in the British patients, 56 ± 11 years in the Spanish patients), the characteristics of the groups were generally similar (sex distribution 71.5% female in the British group, 82.5% female in the Spanish group; mean ± SD disease duration 13.1 ± 9.2 years in the British group, 12.9 ± 7.4 years in the Spanish group; age at disease onset 48 ± 13 years in the British group, 44 ± 12 years in the Spanish group).

As shown in Table 1, the duration of morning stiffness was shorter in the Spanish patients, (absent in 10 British and 21 Spanish patients, <30 minutes in 12 British and 13 Spanish patients, <30 minutes in 41 British and 29 Spanish patients). More Spanish patients were rheumatoid factor positive, and the percentage of patients with rheumatoid nodules was similar. Sjögren’s syndrome was found with similar frequency in both groups. Also, more serious extraarticular manifestations were found only in the British group (2 with digital infarcts, 1 with leg ulcers, 1 with fibrosing alveolitis, 1 with pleural effusion, and 1 with episcleritis; 2 British patients showed symptoms and signs suggestive of pericarditis).

Methodologic differences such as differences in patient selection, and other factors such as differences in treatment, subjectiveness of patients’ perceptions and reports of symptoms, physicians’ subjective criteria, cultural coping strategies, or even climate may have influenced the results. Despite these factors, the consistency between our results and those of Drosos et al is of great interest. In contrast, RA in Greeks is weakly associated with HLA-DR4 and DRw10, as defined at the DNA level (2). In an attempt to identify whether DR4 is a marker of disease severity in Greek RA patients, 84 RA patients were studied. HLA-DR typing was performed by restriction fragment length polymorphism, and subtypes of HLA-DR4 were determined by the polymerase chain reaction. Twenty-one of the 84 patients (25%) were DR4+. There was no difference between DR4+ and DR4− patients with respect to disease duration or functional or anatomic grade. Analysis of the DR4 subtypes showed that Dw15 was the most common variant (9 of 21 patients [43%]). There were no statistically significant differences in clinical manifestations among patients with different DR4 subtypes (3). The same was also true when the clinical picture was correlated with the “shared RA epitope” (QKRAA/QRRAA/RRAAA), which is common to all HLA-DRB1 alleles positively associated with RA (4).

These results suggest that HLA-DR4 is not a disease severity marker in Greek RA patients and further indicate differences in the clinical expression of RA in Greece.

A. A. Drosos, MD
H. M. Moutsopoulos, MD, FACP, FRCP (Edin)
University of Ioannina
Ioannina, Greece
G. S. Panayi, MD, ScD, FRCP
United Medical and Dental Schools
Guy’s Hospital
London, UK

Human IgG anti-DNA antibodies generated with a heteromyeloma cell line reflect serologic findings: comment on the article by Klinman et al

To the Editor:
We read with interest the article by Klinman et al (1). We support the main conclusion that the IgG anti-DNA response of individual MRL/lpr mice is oligoclonal. However, we challenge the hypothesis described in the introduction and discussion sections that hybridoma panels derived from mice are not representative of B cells. Indeed, the